Draft Comparative Effectiveness Review

Number XX

Closing the Quality Gap Series: Comparative Effectiveness of Medication Adherence Interventions

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (http://www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

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We extend our appreciation to our Key Informants and members of our Technical Expert Panel (listed below), all of whom provided thoughtful advice and input during our research process.

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Technical Expert Panel

Technical Experts comprise a multi-disciplinary group of clinical, content, and methodologic experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism

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Closing the Quality Gap Series: Comparative Effectiveness of Medication Adherence Interventions

Structured Abstract

Objectives: To assess the effectiveness of patient, provider, systems, or policy interventions in improving medication adherence, health, adverse events, and health care utilization for chronic health conditions.

Data Sources: MEDLINE, the Cochrane Library. Additional studies were identified from reference lists and technical experts.

Review Methods: Two people independently selected, extracted data from, and rated the risk of bias of relevant trials and systematic reviews. We synthesized the evidence for effectiveness separately for each clinical condition, and within each condition, by type of intervention. We also evaluated the prevalence of intervention components across clinical conditions. We evaluated the effectiveness of interventions for a range of vulnerable populations. Two reviewers graded the strength of evidence (SOE) using established criteria.

Results: A total of 54 trials and three observational studies were included. Fifty-four trials of patient, provider, or systems evaluated 29 types of interventions; we found moderate or low evidence of benefit for medication adherence for 59 percent of these interventions. We found evidence of effective interventions to improve medication adherence for all chronic conditions, with the exception of multiple chronic conditions and multiple sclerosis, and with the most promising interventions being self-management for asthma and collaborative care or case management for depression (rated moderate SOE for short-term outcomes). The most promising gains in health outcomes were for depression case management for symptom improvement and pharmacist-led hypertension approaches for systolic blood pressure (moderate SOE). Evidence from one intervention for collaborative care for depression provided moderate SOE of benefit for patient ratings of quality of care. All other outcomes were rated as low for benefit, low for no benefit, or insufficient. The number of interventions that provide low or moderate strength of evidence progressively decreases for health, health care utilization outcomes, and other distal outcomes.

Three observational studies provide evidence that policy-level interventions that improve prescription drug coverage can have a beneficial effect on adherence to medications used to treat cardiovascular conditions and diabetes (moderate SOE). An evaluation of direct comparisons of intervention components found that shared decisionmaking is more effective than clinical decisionmaking at improving and sustaining improvement in adherence to asthma medication (low SOE). We found evidence of benefit for medication adherence interventions for patients with major depression, severe depression, multiple chronic conditions or depression with hypertension comorbidity, African-American patients with depression and diabetes comorbidity, elderly patients with diabetes, hyperlipidemia, congestive heart failure, or hypertension (low SOE).

Conclusions: Diverse interventions offer promising approaches to improving medication adherence for chronic conditions, particularly for the short term. Evidence on whether these approaches have broad applicability for clinical conditions and populations is limited, as is evidence on long-term medication adherence or health outcomes.

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Executive Summary

Background

Achieving the goals of quantitatively improving the quality and effectiveness of health care for all Americans requires both knowledge and tools. Although medical researchers have demonstrated many efficacious medical treatments to improve health outcomes, a recent Institute of Medicine (IOM) report identified a disquieting discrepancy between present treatment success rates and those thought to be achievable.[1] This gap has been attributed partly to barriers that providers face in implementing best practice guidelines.[1, 2] Patients' adherence to recommended treatment, however, provides an additional explanation for the incongruity between recommended treatment and actual treatment outcomes.

Poor medication adherence is very common.[3, 4] Studies have shown consistently that 20 to 30 percent of medication prescriptions are never filled and that, on average, 50 percent of medications for chronic disease are not taken as prescribed.[5, 6]

This lack of adherence to medications is not only prevalent, but also has dramatic effects on individual and population-level health.[5, 7-16]Moreover, nonadherence has been estimated to cost the U.S. health care system $100 billion annually in direct costs.[5] Strong evidence suggests that benefits attributable to improved self-management of chronic diseases could result in a cost-to-savings ratio of approximately 1:10.[17-23]

Scope and Key Questions

This review seeks to synthesize evidence regarding the efficacy and effectiveness of interventions to improve medication adherence among adults with chronic conditions. This report is part of a larger initiative, *Closing the Quality Gap: Revisiting the State of the Science* (CQG), which builds on the Agency for Healthcare Research and Quality (AHRQ) 2004 to 2007 collection of publications—*Closing the Quality Gap: A Critical Analysis of Quality Improvement Strategies*—that summarized the evidence on quality improvement strategies for chronic conditions.[24] This new series continues to summarize evidence on means to improve quality of care, but it focuses on selected settings, interventions, and clinical conditions. Our report, one of eight in the second series, addresses the comparative effectiveness of adherence intervention strategies, one keystone to improving the gap between potential and realized quality health care. The five key questions (KQs) that are the focus of this review are listed in Table ES-1.

Table ES-2. Key questions (KQs) for this review

KQ 1 **a:** Among patients with chronic diseases with self-administered medication prescribed by a provider, what is the comparative effectiveness of interventions aimed at patients, providers, systems, and combinations of audiences in improving medication adherence? **b:** Is improved medication adherence associated with improvement in patient outcomes?
KQ 2 **a:** Among patients with chronic diseases with self-administered medication prescribed by a provider, what is the comparative effectiveness of policy interventions in improving medication adherence? **b:** Is improved medication adherence associated with improvement in patient outcomes?
KQ 3 **a:** How do medication-adherence intervention characteristics (e.g., mode of delivery, intervention target, intensity) vary? **b:** To what extent do the effects of adherence interventions vary based upon their characteristics?
KQ 4 To what extent do the effects of adherence interventions vary based on differences in vulnerable populations?
KQ 5 What unintended consequences are associated with interventions to improve medication adherence?

The analytic framework we developed to guide the systematic review process is shown in Figure ES-1.

Methods

Topic Refinement

Topics for the Closing the Quality Gap series were solicited from the portfolio leads at AHRQ. Subsequently, the Evidence-based Practice Center (EPC) worked on clarifying the scope of the project. After we generated an analytic framework, preliminary KQs, and preliminary inclusion/exclusion criteria in the form of PICOTS (populations, interventions, comparators, outcomes, settings), our KQs were posted for public comment on AHRQ's Effective Health Care Web site from March 11, 2011, to April 8, 2011. We revised the KQs as needed based on review of the comments and discussion with a five-member Technical Expert Panel (TEP), primarily for readability and greater comprehensiveness.

Literature Search and Review Strategy

To identify articles relevant to each KQ, we conducted targeted searches using MEDLINE®, Cochrane Library, and the Cochrane Central Trials Registry. We reviewed our search strategy with the TEP and supplemented it as needed according to their recommendations. In addition, to avoid retrieval bias, we manually searched the reference lists of pertinent reviews on this topic to look for any relevant citations that might have been missed by our searches.

Two trained members of the research team independently reviewed each of the titles and abstracts. For each article that either or both reviewers chose to include based on the abstract review, two reviewers reviewed their full texts for eligibility against our inclusion/exclusion criteria (Table ES-3). During full-text review, if both reviewers agreed that a study did not meet

Figure ES-1. Analytic Framework

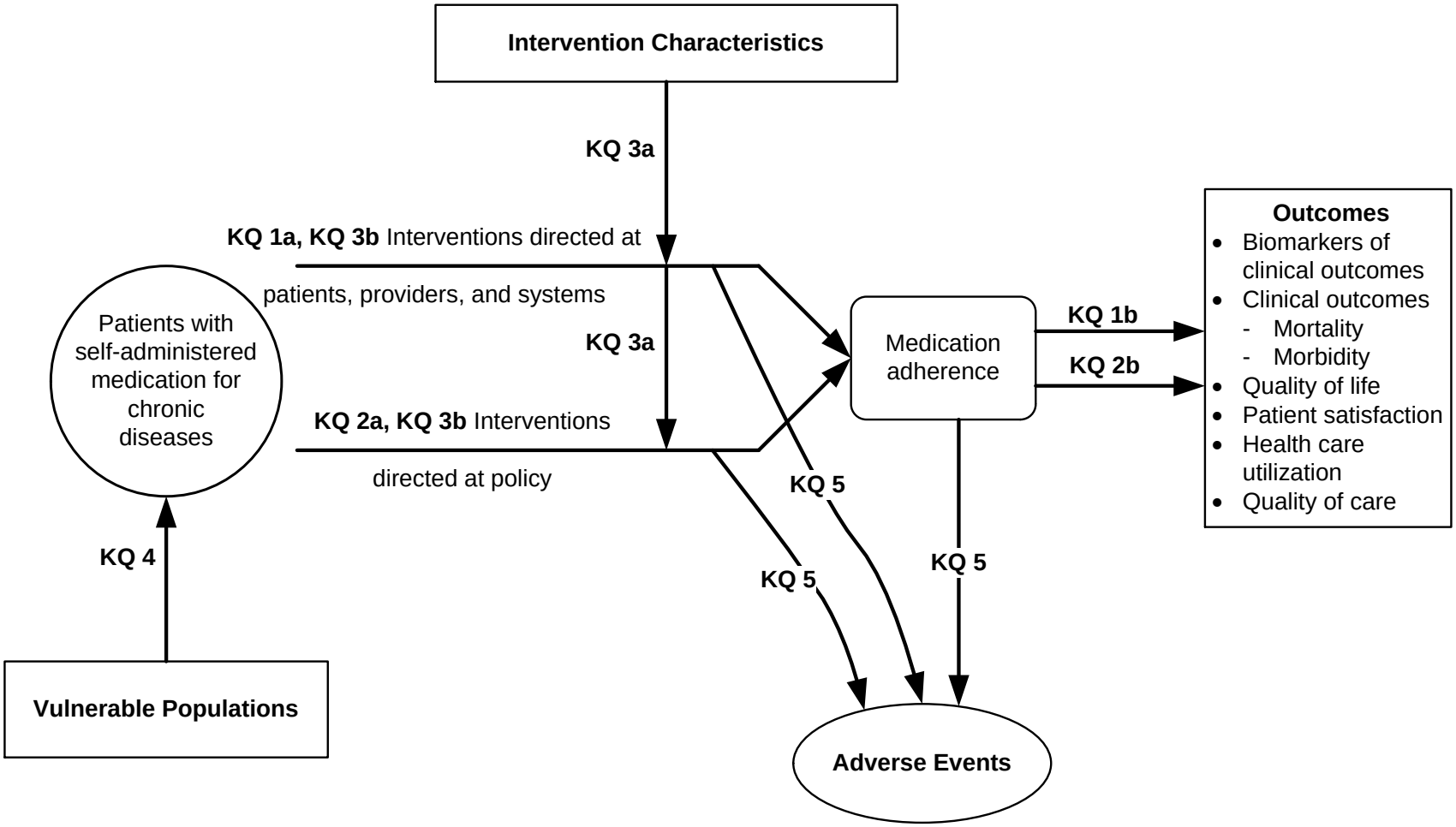


Table ES-3. Inclusion and exclusion criteria

Category	Criteria	
	Inclusion	**Exclusion**
Population	• Adults prescribed self-administered medication for secondary or tertiary prevention of chronic diseases	• Children under the age of 18 (no adults in the study or outcome of interest not stratified by child/adult) • Patients administered medications in hospitals or in offices • Patients undergoing primary prevention • Patients taking over-the-counter medicines not prescribed by a provider • Patients with infectious conditions (e.g., HIV/AIDS, tuberculosis, pelvic inflammatory disease) • Patients with mental illness involving psychosis, mania, or bipolar disorder • Patients on medication to treat substance abuse
Geography	• United States	• All non-United States
Time period	• 1994 to present; searches to be updated after draft report goes out for peer review	• Pre-1994
Length of followup	• No limit	
Settings	• Outpatient primary and specialty care settings • Community-based • Home-based	• Institutional settings (e.g., inpatient care, nursing homes, prisons)
Interventions	• Any intervention for included clinical conditions intended to improve adherence with prescribed, self-administered medications	• Interventions intended to improve compliance with primary prevention measures (e.g., screening, diet, exercise, lifestyle changes)
Outcomes	• Medication adherence • Biomarkers, mortality, morbidity, quality of life, patient satisfaction, health utilization (and associated costs), quality of care for studies with a statistically significant improvement in medication adherence • Adverse events	
Publication language	• English	• All other languages

Admissible evidence for KQ 1 on patient-level, provider-level, or systems-level interventions (study design and other criteria)	• Original research; eligible study designs include:
	  ○ Randomized controlled trials
	  ○ Systematic reviews with or without meta-analyses
		• Nonrandomized controlled trials
		• Observational study designs
		• Case series
		• Case reports
		• Nonsystematic reviews
		• Editorials
		• Letters to the editor
		• Articles rated high risk of bias
		• Studies with historical, rather than concurrent, control groups
		• N < 40

Table ES-2. Inclusion and exclusion criteria (continued)

Category	Criteria	
	Inclusion	Exclusion
Admissible evidence for policy-level interventions (study design and other criteria)	• Original research; eligible study designs include: ○ Randomized controlled trials ○ Systematic reviews with or without meta-analyses ○ Nonrandomized controlled trials ○ Cohort studies ○ Case-control studies ○ Time series ○ Before-after studies	• Cross-sectional studies • Case series • Case reports • Nonsystematic reviews • Editorials • Letters to the editor • Articles rated high risk of bias • N < 40

the eligibility criteria, the study was excluded. Reviewers resolved conflicts by discussion and consensus or by consulting a third member of the review team.

For studies that met our inclusion criteria, a trained reviewer abstracted information into structured evidence tables; a second senior member of the team reviewed all data abstractions for completeness and accuracy.

Risk of Bias Assessment

Two independent reviewers assessed risk of bias (internal validity) for each study using predefined criteria based on those developed by AHRQ[25] and specified in the RTI Item Bank.[26] We resolved disagreements between the two reviewers by consulting an experienced member of the team.

Data Synthesis

KQs 1, 2, 4, and 5 present results categorized by clinical condition. KQ 3 presents results categorized by intervention characteristics. We specified all nonmorbidity data *a priori a*nd elected, based on feedback from our TEP, to collect a comprehensive set of biomarkers and morbidity outcomes rather than make *a priori* judgments about which specific morbidity outcomes to include. In KQ 3, when appropriate data were available, we reported results from direct comparisons of different interventions. We did not attempt indirect comparisons, given the heterogeneity of usual care comparators. We evaluated whether the collected data could be pooled by considering similarity of PICOTS. In instances with three or more similar studies (population, intervention, comparator, outcome), we considered conducting quantitative analyses (i.e., meta-analysis) of the data from those studies. Because quantitative analysis was not appropriate (e.g., due to heterogeneity, insufficient numbers of similar studies, or insufficiency or variation in outcome reporting), we synthesized the data qualitatively. We intended to stratify our analyses and perform subgroup analyses when possible and appropriate. Planned stratifications or categories for subgroup analyses included disease type, intervention characteristics, racial and ethnic minorities, low-health-literacy groups, and the elderly.

Strength of Evidence Grading

We graded the strength of evidence (Table ES-3) for medication adherence, morbidity, mortality, and other long-term health outcomes for KQ 1 and KQ 2, for vulnerable subpopulations (KQ 4), and for harms (KQ5) based on the guidance established for the EPC

program.[27] This approach incorporates four key domains: risk of bias (including study design and aggregate quality), consistency, directness, and precision of the evidence. We also considered plausible confounding for KQ 2, which included observational studies.

Table ES-4. Definitions of the grades of overall strength of evidence

Grade	Definition
High	**High confidence that the evidence reflects the true effect.** Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	**Moderate confidence that the evidence reflects the true effect.** Further research may change our confidence in the estimate of the effect and may change the estimate.
Low	**Low confidence that the evidence reflects the true effect.** Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	**Evidence either is unavailable or does not permit estimation of an effect.**

Source: Owens et al.[27]

Applicability

We assessed the applicability of the evidence following guidance from Atkins and colleagues.[28] We used the PICOTS framework to explore factors that affect or limit applicability.

Results

We provide a summary of results by key question. KQs 1 and 2 synthesize the evidence by clinical condition and then by type of intervention. KQs 3, 4, and 5 synthesize the evidence for all relevant studies for KQ 1 and KQ 2. Detailed descriptions of included studies, key points, detailed synthesis, summary tables, and expanded strength of evidence tables that include the magnitude of effect can be found in the full report. Our summary of results below presents the SOE grades.

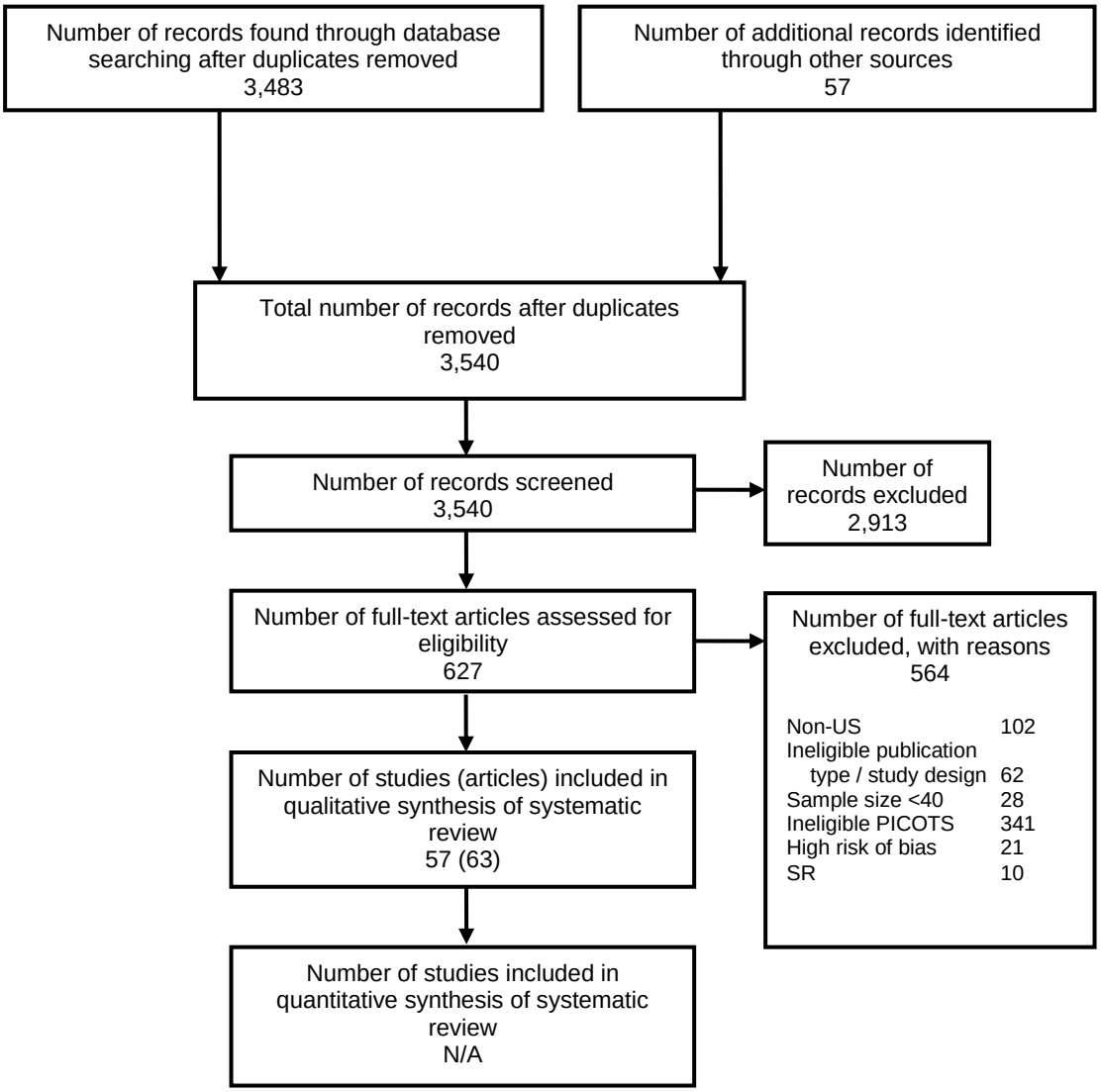
Results of Literature Searches

Figure ES-2 presents our literature search results. Literature searches through April 25, 2011, for the current report identified 3,483 unduplicated citations. Handsearches of systematic reviews and other sources added a total of 57 additional citations. All of these sources produced a total of 3,540 references.

After applying our eligibility and exclusion criteria to titles and abstracts of all identified citations, we obtained full-text copies of 627 published articles. We reapplied our inclusion criteria and excluded 543 of these articles from further review. Twenty-one articles were not included because of a high risk of bias. We included a total of 63 articles for qualitative synthesis. The full report provides appendixes that detail reasons for exclusion at the full-text stage, evidence tables, risk of bias assessments, a list of scales and measures, and detailed SOE tables.

The 63 articles included in this review represent 57 studies. Of the 63 included articles, 60 were randomized controlled trials or associated articles, and 3 were observational studies. Among the trials, 49 used a parallel randomization scheme, while 11 used cluster randomization. Fifty-four of the included articles were assessed as medium risk of bias, and 9 met the standards for low risk of bias.

Figure ES-2. Disposition of articles (PRISMA figure)



Key Findings and Strength of Evidence

KQ 1: Effect of Patient, Provider, or Systems Interventions on Medication Adherence and Other Outcomes

Overview

Overall, the evidence from 54 trials suggests that numerous pathways provide opportunities to improve medication adherence across clinical conditions. These include relatively low-cost, low-intensity telephone and mail interventions. They also include some relatively intense interventions, such as care coordination and case management (requiring close and ongoing monitoring of patients) and collaborative care (requiring a restructuring of typical U.S.-based health care delivery). Despite evidence suggesting that several interventions offer promising approaches to improving medication adherence, evidence exists for only a subset of these effective interventions showing that the improved adherence is accompanied by improvements in other outcomes, such as biomarkers, mortality, morbidity, quality of life, patient satisfaction, health care utilization, costs, or quality of care.

Findings Specific to Clinical Conditions

The volume of evidence varies sharply by clinical condition (Table ES-4). We found the greatest volume of evidence for hypertension and depression, followed by hyperlipidemia, asthma, and diabetes. We did not find a substantial body of evidence testing varied approaches to inform several clinical conditions. Specifically, we found single-study bodies of evidence for myocardial infarction, glaucoma, and multiple sclerosis. For musculoskeletal diseases, we found two studies that used interventions with common features. We found no eligible studies for cancer; reasons likely include the restriction of the scope of the review to patient-administered medications and outpatient settings. We found no eligible studies that explicitly focused on patients with adherence problems due to polypharmacy, although a few studies included patients with two or more conditions and assessed adherence to more than one medication.

Findings Specific to Interventions

Among the clinical conditions included in this review for which we identified multiple intervention approaches, we found the most consistent evidence of improved medication adherence outcomes for hypertension, hyperlipidemia, congestive heart failure, and depression. We generally graded interventions as being beneficial with low to moderate strength of evidence, depending upon the specific type of intervention; these clinical conditions also included some interventions for which we found insufficient evidence. The evidence was less consistent for asthma and diabetes. For asthma, some interventions, such as self-management approaches or shared decisionmaking, were effective in improving medication adherence, but other approaches, such as offering health care providers access to patient adherence data, suggested evidence of no benefit. For diabetes, the only trials that indicated evidence of benefit used care coordination and collaborative care approaches; all other approaches did not show evidence of benefit. We found the least consistent evidence of improvement in medication adherence for multiple chronic conditions: three trials, using pharmacist-based outreach, education, and problem solving approaches, provided evidence of no benefit, and another trial, using case management, offered insufficient evidence.

Table ES-5. Number of included studies by clinical condition, intervention, and comparator

Clinical Condition	Intervention	Comparator	Number of Studies
Diabetes[29-31]	Care coordination and collaborative care	Usual care	3
Diabetes\hyperlipidemia[32-34]	Decision aids	Educational interventions	2
Diabetes[35]	Health coaching	Usual care	1
Diabetes[36]	Social support	Educational interventions	1
Hyperlipidemia[37-39]	Telephone-based interventions (e.g., reminders, active problem management, tailored support)	Usual care or less intense intervention	3
Hyperlipidemia[38, 40, 41]	Mail-based education (e.g., standard videos, tailored print)	Usual care	2
Hyperlipidemia[42]	Collaborative care	Usual care	1
Hyperlipidemia[43]	Pharmacist-led multicomponent (for 12 months)	Pharmacist intervention (for 6 months)	1
Hypertension[44-49]	Telephone-based education	Usual care	5
Hypertension[43, 50-54]	Pharmacist-led intervention (e.g., education, collaborative care, clinic)	Usual care or less intense intervention	5
Hypertension[41, 55]	Mail-based education (e.g., standard videos, tailored print)	Usual care	2
Hypertension[29, 36, 56]	Other interventions (e.g., collaborative care, nurse support, blister packing)	Usual care	3
Congestive heart failure[57]	Video and telephone reminders	Usual care	1
Congestive heart failure[58]	Pharmacist-led multicomponent	Usual care	1
Congestive heart failure[59]	Multisetting, multidisciplinary	Usual care	1
Congestive heart failure[60]	Patient access to medical records and messaging system	Usual care	1
Myocardial infarction[61]	Mail-based communication to patients and providers about importance of medication adherence	Usual care	1
Asthma[62-66]	Self-management	Usual care	5
Asthma[67, 68]	Pharmacist or physician access to patient adherence information	Usual care or pharmacist training	2
Asthma[69]	Shared decisionmaking	Clinician decisionmaking or usual care	1
Depression[70, 71]	Telemonitoring	Usual care	2
Depression[30, 44, 72-74]	Case management	Usual care	3
Depression[29, 75-80]	Collaborative care	Usual care	6
Depression[81]	Reminder letters to nonadherent patients and monthly lists of nonadherent patients to providers	Usual care	1
Glaucoma[82]	Multicomponent	Usual care	1
Multiple sclerosis[83]	Software-based telephone counseling	Usual care	1
Musculoskeletal diseases[84, 85]	Case management	Usual care	2
Multiple or unspecified chronic conditions[86-88]	Pharmacist-based outreach, education, and problem solving	Usual care	3
Multiple or unspecified chronic conditions[89]	Case management	Usual care	1

Some intervention approaches that were tested across multiple clinical conditions include decision aids, case management, care coordination or collaborative care, telephone-based support, pharmacist-led multicomponent approaches, and mail-based education. One intervention, shared decisionmaking, has been tested in a single clinical area, asthma, with a

single trial; without additional evidence, its widespread applicability is difficult to judge but it may well hold promise.

We note that these categories served as shorthand for one or more key elements of very diverse interventions. For instance, of the two trials categorized as interventions that gave health care providers access to patient adherence data, one included a substantial pharmaceutical care program, while the other did not. These examples illustrate that while the inductive approach we used to identify types of interventions allowed us to group interventions, it limited our ability to make conclusions about the effectiveness of specific intervention features. To address this limitation, KQ 3 offers further insights on common elements across these interventions.

Findings Specific to Outcomes

Table ES-6 through Table ES-9 present a summary of strength-of-evidence findings for medication adherence (Table ES-6), biomarkers and morbidity (Table ES-7), quality of life and patient satisfaction (Table ES-8), and lastly, health utilization, costs, and quality of care (Table ES-9). We do not present a table for mortality: we found a single study providing insufficient evidence for patient access to medical records for congestive heart failure. Fifty-four trials provided evidence on 29 types of interventions; of these, 59 percent provided moderate or low evidence of benefit for medication adherence. The number of interventions that provide low or moderate strength of evidence progressively decreases for health, health care utilization outcomes, and other distal outcomes.

We found evidence of effective interventions to improve medication adherence for all chronic conditions, with the exception of multiple chronic conditions and multiple sclerosis (Table ES-6).The most promising interventions were self-management for asthma (for short-term outcomes), and collaborative care or case management for depression (rated moderate strength of evidence). For all other interventions, we found evidence of lower strength for medication adherence. Most often, we found insufficient evidence to judge benefit or lack of benefit; for some interventions we found low strength of evidence suggesting benefit for medication adherence; and for a few interventions, we found low strength of evidence of no benefit for medication adherence..

The most promising gains in health outcomes (that is, outcomes rated as moderate strength of evidence) were for depression case management for symptom improvement and pharmacist-led hypertension approaches for systolic blood pressure (Table ES-6). We rated evidence from all other interventions as low for benefit or insufficient. Our evaluation of evidence for patient satisfaction and quality of life did not reveal any evidence of moderate strength (Table ES-7). Evidence from one intervention for collaborative care for depression provided moderate strength of evidence of benefit for patient ratings of quality of care (Table ES-8). For all other interventions, we either found low strength of evidence that the intervention provided benefit for health outcomes or we judged the evidence as being insufficient to evaluate benefit or lack of benefit.

Table ES-6. Summary of evidence for medication adherence

Strength of Evidence	Clinical Condition	Intervention
Benefit from intervention: moderate strength of evidence	Asthma[62-66]	Self-management
	Depression[76-79]	Collaborative care (telephone+in-person visits)
	Depression[30, 44, 72-74]	Case management
Benefit from intervention: low strength of evidence	Diabetes[29-31]	Care coordination and collaborative care
	Hyperlipidemia[37-39]	Telephone-based interventions (e.g., reminders, active problem management, tailored support)
	Hyperlipidemia[38, 40, 41]	Mail-based education (e.g., standard videos, tailored print)
	Hypertension[44-49]	Telephone-based education
	Hypertension[43, 50-54]	Pharmacist-led intervention (e.g., education, collaborative care, clinic)
	Hypertension[41, 55]	Mail-based education (e.g., standard videos, tailored print)
	Congestive heart failure[57]	Video and telephone reminders
	Congestive heart failure[58]	Pharmacist-led multicomponent
	Congestive heart failure[59]	Case management (multisetting)
	Myocardial infarction[61] [a]	Mail-based communication to patients and providers about importance of medication adherence
	Asthma[69]	Shared decisionmaking
	Depression[81]	Reminder letters to nonadherent patients and monthly lists of nonadherent patients to providers
	Glaucoma[82]	Multicomponent including education, reminders, and dosing aid
	Multiple sclerosis[83]	Software-based telephone counseling
No benefit from intervention: low strength of evidence	Asthma[67, 68]	Pharmacist or physician access to patient adherence information
	Multiple or unspecified chronic conditions[86-88]	Pharmacist-based outreach, education, and problem solving
Insufficient evidence	Diabetes/hyperlipidemia[32-34]	Statin decision aids
	Diabetes[35]	Health coaching
	Diabetes[36]	Social support
	Hyperlipidemia[42]	Collaborative care
	Hyperlipidemia[43]	Pharmacist-led multicomponent (for 12 months)
	Hypertension[29, 36, 56]	Other interventions (e.g., collaborative care, nurse support, blister packing)
	Congestive heart failure[60]	Patient access to medical records and messaging system
	Myocardial infarction[61] [b]	Mail-based communication to patients and providers about importance of medication adherence
	Depression[29, 75, 80]	Collaborative care (depression+HIV, depression+diabetes, telephone-only)
	Depression[70, 71]	Telemonitoring
	Musculoskeletal diseases[84, 85]	Case management
	Multiple or unspecified chronic conditions[89]	Case management

[a] Low for adherence

[b] Insufficient for persistence

Table ES-7. Summary of evidence for patient health outcomes: biomarkers and morbidity

Strength of Evidence Grade	Clinical Condition	Intervention	Specific Outcome(s)
Benefit from intervention: moderate strength of evidence	Hypertension	Pharmacist-led intervention (e.g., education, collaborative care, clinic)	Systolic blood pressure
	Depression	Case management	Depressive symptoms
Benefit from intervention: low strength of evidence	Diabetes	Care coordination and collaborative care	HBA1c Depressive symptoms
	Hypertension	Telephone-based education	Diastolic and systolic blood pressure
	Hypertension	Pharmacist-led intervention (e.g., education, collaborative care, clinic)	Diastolic blood pressure
	Asthma	Shared decisionmaking	Pulmonary function Asthma symptoms
	Depression	Case management	Diastolic and systolic blood pressure HbA1c
	Depression	Collaborative care	Major depression Moderately depressed
Insufficient	Diabetes	Social support	HbA1c
	Asthma	Self-management	Pulmonary function and inflammation markers Asthma symptoms
	Depression	Case management	Self-reported disability
	Depression	Collaborative care	Minor depression Severely depressed
	Glaucoma	Multicomponent including education, reminders, and dosing aid	Intraocular pressure

Note: Included evidence is limited to studies that found a benefit for medication adherence

Abbreviations: HbA1c: glycosylated hemoglobin; HIV: Human immunodeficiency virus

Table ES-8. Summary of evidence for patient quality of life and patient satisfaction

Strength of Evidence Grade	Clinical Condition	Intervention	Specific Outcome(s)
Benefit from intervention: low strength of evidence	Diabetes/hyperlipidemia	Statin decision aids	Patient satisfaction
	Diabetes	Social support	Patient satisfaction
	Depression	Collaborative care	Patient satisfaction
	Congestive heart failure	Pharmacist-led multicomponent	Patient satisfaction
	Asthma	Shared decisionmaking	Quality of life
No benefit from intervention: low strength of evidence	Asthma	Self-management	Quality of life
Insufficient	Depression	Collaborative care	Quality of life
	Hyperlipidemia	Pharmacist-led multicomponent (for 12 months)	Patient satisfaction
	Hypertension	Pharmacist-led intervention (e.g., education, collaborative care, clinic)	Quality of life Patient satisfaction
	Hypertension	Other interventions (e.g., collaborative care, nurse support, blister packing)	Patient satisfaction
	Congestive heart failure	Video and telephone reminders	Quality of life
	Congestive heart failure	Pharmacist-led multicomponent	Quality of life
	Congestive heart failure	Patient access to medical records and messaging system	Quality of life Patient satisfaction
	Musculoskeletal diseases	Case management	Patient satisfaction

Note: Included evidence is limited to studies that found a benefit for medication adherence

Table ES-9. Summary of evidence for health utilization, costs, and quality of care

Strength of evidence grade	Clinical condition	Intervention	Specific outcome(s)
Benefit from intervention: moderate strength of evidence	Depression	Collaborative care	Quality of care
Benefit from intervention: low strength of evidence	Hypertension	Pharmacist-led intervention (e.g., education, collaborative care, clinic)	Hospital visits and other contacts
	Congestive heart failure	Pharmacist-led multicomponent	All-cause ED visits and all-cause ED visits + hospitalizations
	Asthma	Shared decisionmaking	Health utilization
Insufficient	Hypertension	Pharmacist-led intervention (e.g., education, collaborative care, clinic)	Other measures of health utilization
	Congestive heart failure	Pharmacist-led multicomponent	All-cause ED visits and all-cause ED visits + hospitalizations Other measures of health utilization Costs
	Congestive heart failure	Case management (multisetting)	Health utilization
	Congestive heart failure	Patient access to medical records and messaging system	Health utilization
	Depression	Collaborative care	Health utilization Costs

Note: Included evidence is limited to studies that found a benefit for medication adherence

Abbreviations: ED: emergency department

KQ 2: Effect of Policy Interventions on Medication Adherence and Other Outcomes

Only three studies evaluated the effects of policy-level interventions on medication adherence. These studies addressed adherence to medications used to treat cardiovascular disease, diabetes, and respiratory conditions. All three studies used retrospective cohort designs and assessed medication adherence using insurance claims data to measure either the medication possession ratio (MPR) or proportion of days covered (PDC). The use of similar adherence measures across the studies facilitates comparing their results. All three studies evaluated policy-level interventions that reduced patient out-of-pocket expenses for prescription medications, either through reduced medication copayments or improved prescription drug coverage. The study by Zhang and colleagues evaluated the impact of Medicare Part D on medication adherence among groups of older adults who had different levels of prescription drug coverage prior to implementation of Medicare Part D.[90] This study found a large improvement in adherence among individuals who had no prescription drug coverage prior to Medicare Part D and smaller improvements among individuals with some prior coverage, but whose out-of-pocket expenses were reduced following Medicare Part D implementation.

Both studies evaluating the impact of reduced copayment on medication adherence also found statistically significant between-group differences in adherence to medications used to treat cardiovascular conditions and diabetes, favoring the group who had their copayment reduced. However, we find these differences somewhat difficult to interpret because medication

adherence decreased over time in all groups in both of these studies. Still, the magnitude of effects observed in these two studies were similar to those observed by Zhang and colleagues among individuals who had some prescription drug coverage prior to Medicare Part D, but who experienced a reduction in out-of-pocket medication expenses following its implementation.[90] Therefore, we concluded that there is moderate strength of evidence indicating that policy-level interventions that reduce patient out-of-pocket expenses can have a beneficial effect on adherence to medications used to treat cardiovascular conditions and diabetes (Table ES-10).

Only one study evaluated the effects of policy-level interventions on adherence to medications used to treat respiratory conditions. This study found no effect on medication adherence. Therefore, we concluded that there is insufficient evidence to draw conclusions for the effectiveness of these types of interventions in this clinical area (Table ES-10).

None of the studies examined the effect of policy-level interventions on more distal outcomes (e.g., morbidity, mortality, health service utilization). We consider this a major gap in the literature.

Table ES-10. Summary of evidence for policy-level interventions

Clinical Condition	Intervention	Comparator	Number of Studies	Medication Adherence	Other Outcomes
Cardiovascular disease[90-92]	Improved prescription drug coverage	Unchanged prescription drug coverage	3	Benefit: moderate SOE	No evidence
Diabetes[90, 91]	Improved prescription drug coverage	Unchanged prescription drug coverage	2	Benefit: moderate SOE	No evidence
Respiratory conditions[91]	Reduced medication copay	Unchanged medication copay	1	Insufficient SOE	No evidence

SOE, strength of evidence.

KQ 3a: Characteristics of Medication Adherence

Overall, the extreme heterogeneity of terminology used to describe medication adherence interventions in the studies reviewed hindered the ability to compare effects of different features of the interventions across studies and across diseases. Moreover, heterogeneity of the interventions themselves made identification of "intervention type" clusters challenging. Most, but not all, studies provided information, though not in a standardized manner, about six key intervention characteristics, which included the target(s), the agent(s), and the mode(s) of the intervention, as well as their intensity, duration, and components. These characteristics provided a framework by which we could describe the interventions. For example, for the intervention target, a little over half of the interventions were aimed at a combination of multiple targets, whereas nearly 40 percent targeted only patients. Similarly, for the agent of intervention delivery, a pharmacist, physician, or nurse delivered about half of the interventions. About half of the interventions involved at least some face-to-face delivery of the program.

In addition to characterizing the interventions for each of these six key features, we also identified some general patterns of combinations of the six features. For example, while interventions varied in the number of contacts (range of 1 to30), those with more contacts tended to involve phone contact. Similarly, certain intervention components, such as facilitation and knowledge-based components affecting the delivery of medical information, were commonly used across most interventions, whereas others, such as motivational interviewing and contingent rewards were used less commonly. Similarly, we noted a greater frequency of combining

awareness-raising activities with knowledge delivery among nurse-delivered compared with pharmacist- and physician-delivered interventions. The components of the intervention were the least well-characterized aspect, although often the feature that most meaningfully distinguished them. Some intervention types, such as decision aids, were not captured by existing taxonomies of adherence intervention components.

KQ 3b: Direct Comparisons of Medication Adherence Intervention Components

The vast majority of studies compared a multicomponent intervention to a "usual care" control arm. Few studies directly compared one feature of an intervention to another feature to determine which aspects of the intervention had the most effect on outcomes. Among the three studies that conducted this kind of comparison, each compared different aspects of different interventions. As a result, we could not pool across the three studies. Within those three studies, one demonstrated that shared decisionmaking had a greater effect on adherence to asthma medications than did a clinical decision-making approach, while both were more efficacious than usual care. Moreover, the effects of shared decisionmaking on adherence lasted up to 2 years whereas those due to clinical decisionmaking had attenuated at that point. Another study, conducted among patients with congestive heart failure, directly compared two different delivery modes (telephone versus videophone). This study found no difference between the two delivery modes regarding improvement in adherence: both were superior to usual care. Another study directly compared the agent of delivery (physician versus research staff) using the same mode (face-to-face) to deliver a decision aid among patients with diabetes deciding whether to take statins to lower their risk of cardiovascular disease. The effects were the same regardless of who delivered them: the decision aid had greater improvement on adherence than usual care, regardless of who delivered the aid.

Mode of delivery appears to have been an important feature only in certain settings. Moreover, agent of delivery does not appear to be important in the setting studied for the decision aid. However, shared decisionmaking seemed to be more effective than clinical decisionmaking at improving and sustaining improvement in adherence to asthma medication. Shared decisionmaking also appeared to improve pulmonary function tests when compared with clinical decisionmaking but did not improve quality of life or health care utilization; we rated this evidence as having low strength (Table ES-11).

Table ES-11. Direct comparisons of medication adherence intervention components: strength of evidence summary table

Clinical condition Citations	Intervention	Comparator	#	Medication Adherence	Mortality	Biomarkers	Morbidity	Quality of Life	Healthcare Utilization
Asthma[69]	Shared decisionmaking	Clinician decisionmaking	1	Benefit: low SOE	No evidence	Benefit: low SOE	Insufficient	No benefit: Low SOE	No benefit: Low SOE
Congestive Heart Failure[57]	Telephone reminders	Video reminders	1	Insufficient	No evidence	No evidence	No evidence	No evidence	No evidence
Diabetes[32]	Decision aids delivered by clinician	Decision aids delivered by research staff	1	Insufficient	No evidence	No evidence	No evidence	No evidence	No evidence

SOE, strength of evidence.

KQ 4: Outcomes for Vulnerable Populations

We searched for evidence on a broad set of vulnerable populations and found varying degrees of strength of evidence. For certain vulnerable subgroups (specifically for patients with major depression, severe depression, multiple chronic conditions or depression with hypertension comorbidity, African-American patients with depression and diabetes comorbidity, elderly patients with diabetes, hyperlipidemia, congestive heart failure or hypertension) we determined that there was low strength of evidence of interventions having a positive impact on medication adherence. We found low strength of evidence of no benefit of interventions on adherence for interventions dealing with patients who had depression with HIV comorbidity, and diabetes with depression comorbidity. The low number of studies and limited sample size of included studies curtailed our confidence in the strength of evidence. For some vulnerable subgroups, including low-income, underinsured or populations with low health literacy, we did not find any evidence.

KQ 5: Adverse Effects

Our review of studies that examined adverse events or harms associated with interventions aimed at improving adherence did not find any indication that these interventions result in any unintended consequences for patients. However, we found only three relevant studies, and the level of heterogeneity among these studies in terms of the intervention and outcomes was so significant that we determined insufficient evidence existed to reach definitive conclusions.

Discussion

Key Findings and Strength of Evidence

We found evidence of effective interventions to improve medication adherence for most chronic conditions, suggesting that medication adherence to chronic medication can be improved through intervening with patients, providers, health systems, or policy and that a broad range of approaches can work. Adherence is the result of a combination of patient, provider, and policy factors; hence, most interventions we identified were multifactorial: over half were aimed at multiple targets and most had multiple components, including several with multiple delivery modes. In other words, there is no one magic bullet for medication adherence. We found the strongest evidence for enhancing adherence with self-management of asthma (for short-term outcomes) and collaborative care or case management for depression. We found the strongest evidence with depression case management for depression symptom improvement and pharmacist-led hypertension approaches for systolic blood pressure improvement. These findings suggest that clinicians should consider adherence interventions for their chronically ill patients, particularly self-management for asthma, case management for depression, and involvement of a pharmacist trained in adherence management for care of hypertension.

Clinicians and policymakers should keep in mind that we found very little evidence of the relationship of improved medication adherence and adverse events, although what we found suggests that improving adherence does not increase the incidence of adverse events. This was the first review we are aware of that systematically reviewed information on adverse events and so provides promising information that should be confirmed in future studies and reviews.

The lack of studies evaluating potential mechanisms that link improved adherence to other outcomes limits policymakers' and clinicians' ability to use an "a la carte" approach to implementing components of complex interventions to enhance patients' medication adherence.

Therefore, future studies need to do a better job not only of clearly describing each component of their intervention but also of designing studies and conducting analyses that can identify which components are driving the effects of the intervention.

Poor medication adherence is known to result in large upstream health care costs. An important finding for policymakers contemplating changes in health policy is our assessment of moderate evidence, from three consistent studies, that reducing patients' out-of-pocket costs can improve their medication-taking behavior. Policies that enhance patient adherence by easing patient copayments or other patient paid medication expenses may prove highly cost-effective. Cost-effectiveness studies that assess the long-term effects of such policies could be beneficial to policymakers.

Applicability

The interventions included in this review were not highly selective nor did they limit themselves to narrow or unrepresentative disease severity. An additional factor contributing to overall applicability includes the large variety of clinical conditions.. The interventions themselves spanned the range from minimalist to intense and minimalist, although evidence often came from small studies. Because this diversity in types of clinical condition and interventions is not supported by replication of studies in different settings, the findings are limited in their applicability. Another limitation to the applicability of the evidence comes from the complexity of multicomponent interventions. Studies did not generally provide information on the extent to which active ingredients in interventions were identified, operationalized, and translated into instructions and manuals for replication. The degree to which these interventions require fidelity to protocol when implemented in nontrial settings is also unclear, further limiting the applicability of the evidence.

Limitations

The constraints for population and setting we imposed on the systematic review serve as limitations to the applicability of the review. As noted earlier, we did not review the evidence on populations with human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), mania, bipolar disorder, or substance abuse. Interventions for these excluded clinical conditions may apply to the conditions that we included in our review. Another limitation is that of setting: we excluded non-English and non-U.S. studies. This criterion likely substantially decreased the pool of eligible studies but their applicability to the United States is unclear. Finally, our inductive approach to categorizing interventions for KQ 1, in the absence of an overarching taxonomy, resulted in intervention labels that did not fully describe or account for heterogeneity within and across clinical areas. This approach limits our ability to make statements about the effectiveness of interventions across clinical areas.

Research Gaps

Our review identified several gaps in the literature that may be filled by future research efforts. In many disease areas for KQ1, interventions and adherence measures were heterogeneous, which limited the ability to pool results from studies. The use of more standardized, objective adherence outcomes in future research could help results from studies become more interpretable in the context of other adherence studies. In addition, a lack of focus on mediating relationships through which the interventions acted on medication adherence

limited the conclusions that could be drawn about the efficacy of specific intervention features. Moreover, while some studies showed that interventions improved adherence, only a few had large effects on adherence. Hence, future studies could be designed to identify how to enhance the effects of efficacious interventions, such as by using a factorial design that combines efficacious interventions and can assess both additive and multiplicative effects. At a minimum, the use of SQUIRE guidelines will improve the quality of reporting so that future studies of complex interventions routinely clarify the mechanisms by which intervention components are expected to cause change, the course of the implementation, and the success of tests of the mechanism of action.[93] Although many studies did assess some health outcomes, the inclusion of long-term health outcomes in all studies of adherence would enhance capacity to assess overall significance of adherence interventions. This would also facilitate cost-effectiveness analyses of such interventions. Detailed research gaps by clinical area and key question can be found in the full report.

We suggest that future studies of medication adherence interventions adopt a standardized manner for describing such interventions that includes a clear report of the intended targets of the intervention, all agents, and modes of delivery using the categories we have identified here. Moreover, we believe that it would be quite simple for studies to describe the intensity and duration of all interventions in a similarly standardized manner that included the total number and type of contacts, the total amount of time for each contact, the frequency of the contacts, and the duration of calendar time over which the contacts are delivered. For interventions that do not involve contacts per se, such as policy changes, these variables would be categorized as "not applicable." Much as specifications of CONSORT statement[94] enhanced capacity to compare and pool clinical trial results across studies, such a simple step as standardizing this reporting descriptions of interventions would go a long way to enhancing capacity to understand the effects of different aspects of these intervention.

Conclusions

Despite heterogeneity of adherence measurement, interventions tested, and characterization of interventions, we found a few nonpolicy-level interventions for which there was moderate evidence of benefit to improve medication adherence and health outcomes: self-management for short-term improvement in adherence to asthma medications; collaborative care or case management for short-term improvement of adherence to depression medications and symptoms; and pharmacist-led hypertension approaches for systolic blood pressure improvement. There was also moderate strength of evidence that policy-level interventions that reduce the amount of out-of-pocket expenses incurred by patients improves medication adherence. We found low strength of evidence for many other interventions; these diverse groups of approaches offer promise but require more research to establish greater strength of evidence. Less evidence existed, however, for interventions that benefited health outcomes along with medication adherence. Several reviews that researchers have conducted over the last two decades along with this one confirm that medication adherence can be improved via intervention. At this stage, new studies need to be asking "What specific intervention element or elements work best for improving medication adherence?" and "How can we further enhance medication adherence interventions to improve health outcomes?"

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Introduction

Background

Achieving the goals of quantitatively improving the quality and effectiveness of health care for all Americans requires both knowledge and tools. Although medical researchers have demonstrated many efficacious medical treatments to improve health outcomes, a recent Institute of Medicine (IOM) report identified a disquieting discrepancy between present treatment success rates and those thought to be achievable.[1] This gap has been attributed partly to barriers that providers face in implementing best practice guidelines.[1, 2] Patients' adherence to recommended treatment, however, provides an additional explanation for the incongruity between recommended treatment and actual treatment outcomes.

Medication adherence in particular is defined as "the extent to which patients take medication as prescribed by their health care providers."[3 (p. 487)] The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Medication Compliance and Persistence Workgroup, as well as other medication adherence experts, recently recommended distinguishing between two different types of nonadherence that may have distinctive causes and likely have different effects on health outcomes. Specifically, increasing emphasis has been placed on differentiating medication persistence from medication adherence.[4-6] In this view, medication adherence refers to the patient's conformance with the provider's recommendation with respect to *timing, dosage,* and *frequency* of medication taking during the prescribed length of time.[4, 5] In contrast, persistence refers to the act of continuing the treatment for the prescribed *duration* and may be defined as the total length of time a patient takes a medication, demarcated by the time between first and last dose.[5, 6] In the same sense that health outcomes may be improved by enhancing provider implementation of best practice guidelines, they may also be improved by helping patients better adhere to and persist with recommended treatment.[7-9]

Since 1950, pharmacological management of many acute and chronic health problems has advanced rapidly; among the conditions benefiting from this progress are diabetes, hypertension, hypercholesterolemia, asthma, and cardiovascular disease[10-14] When left untreated or undertreated, particularly in the setting of chronic illness,[15] these conditions often lead to complications (e.g., myocardial infarction, stroke, kidney failure, immune compromise) that decrease patients' quality of life and increase their risk of death.[16]

Despite the established capacity for many medications to reduce both mortality and morbidity, many patients do not use their medications as recommended by health care providers.[3, 8, 16-18] Although the specific consequences of suboptimal adherence to medications vary greatly, depending on the condition treated and the prescribed treatment, poor adherence clearly poses a threat to the health of the U.S. population[18, 19] that must be addressed to reduce the gap between potential and actual health care quality. Moreover, researchers have suggested that factors affecting adherence differ, depending on the chronicity of the illness.[15, 20, 21] Glasgow and colleagues have proposed that, as a result, chronic illness cannot be addressed adequately with a traditional, directive acute care model.[15] Instead, they argue, supporting adherence to treatment of chronic illness requires active engagement of patients in their treatment over time. This view, in turn, calls for using a newer, chronic care model.

Moreover, as described in the following section discussing health disparities, medication adherence is particularly salient for several vulnerable populations of interest to the Agency for Healthcare Research and Quality (AHRQ) and the IOM, including ethnic minorities, people with low literacy, and the elderly. The World Health Organization (WHO) has pointed out that

economically disadvantaged groups not only have higher incidence and prevalence of many chronic illnesses than other populations, but that they also face greater barriers to medication taking than those who are more advantaged.[22] Thus, understanding approaches to enhancing medication adherence may provide a way to reduce health disparities. Because medication adherence is becoming more recognized as an important issue in health care quality, treatment guidelines often include recommendations for providers to consider adherence.

Guidelines and recommendations released over the past 5 years (from 2006 onward) that address medication adherence-related issues are predominantly disease specific and focus on a particular condition, such as depression, asthma, overweight/obesity, and HIV/AIDS. Furthermore, adherence is not the focus of these guidelines, but rather one among several issues discussed in the area of disease treatment and management. Recent disease-specific recommendations include those published by the U.S. Department of Veterans Affairs and the New York State Department of Health. Guidelines from the National Collaborating Centre for Primary Care on behalf of the United Kingdom-based National Institute for Health and Clinical Excellence (NICE) provide recommendations pertaining to medication adherence that are not disease specific.[23-27] Details regarding these guidelines are shown in Table 1.

Table 1. Guidelines for medication adherence

Title	Source	Date
Medicines Adherence: Involving Patients in Decisions About Prescribed Medicines and Supporting Adherence[26]	Developed by the National Collaborating Centre for Primary Care on behalf of the National Institute for Health and Clinical Excellence (United Kingdom)	2009
VA/DoD Clinical Practice Guideline for Management of Asthma in Children and Adults[24]	U.S. Department of Veterans Affairs/ U.S. Department of Defense	2009
VA/DoD Clinical Practice Guideline for Screening and Management of Overweight and Obesity[25]	U.S. Department of Veterans Affairs/ U.S. Department of Defense	2006
VA/DoD Clinical Practice Guideline for Management of Major Depressive Disorder[23]	U.S. Department of Veterans Affairs/ U.S. Department of Defense	2009
Adherence to Antiretroviral Therapy Among HIV-Infected Patients With Mental Health Disorders[27]	New York State Department of Health	2006

Abbreviations: VA, U.S. Department of Veterans Affairs; DoD, U.S. Department of Defense

Prevalence and Burden

Poor medication adherence is very common.[3, 18] Studies have shown consistently that 20 to 30 percent of medication prescriptions are never filled and that, on average, 50 percent of medications for chronic disease are not taken as prescribed.[19, 28] A meta-analysis of studies examining the prevalence of medication nonadherence estimated that 21 percent of patients do not take their medications as recommended.[16] Further, nonadherence tends to occur with greater frequency when patients use medications to treat asymptomatic, chronic conditions such as hypertension and hypercholesterolemia. The literature suggests that 20 to 75 percent of patients who are prescribed medications for these conditions are not adhering to the regimen at their 1-year followup.[3, 17]

This lack of adherence to medications is not only prevalent, but also has dramatic effects on individual and population-level health. In fact, the WHO identified medication adherence as a primary determinant of treatment effectiveness.[22, 29-31] In the United States, the lack of adherence to medications has been estimated to cause approximately 125,000 deaths, at least 10 percent of hospital admissions,[19] and substantial worsening of morbidity and mortality.[16, 32] For example,

poor adherence, which includes though is not limited to medication adherence has been identified as the primary cause of inadequate blood pressure control[33] and of complications of hypertension[34-36] and poor treatment outcomes in depressed patients.

Moreover, nonadherence has been estimated to cost the U.S. health care system $100 billion annually in direct costs.[19] One study found that the direct costs of complications attributable to poor control of diabetes in Europe were three to four times higher than the costs among patients with good control.[37] Strong evidence suggests that benefits attributable to improved self-management of chronic diseases could result in a cost-to-savings ratio of approximately 1:10.[38-44]

Although experts agree that poor adherence to medications is a widespread phenomenon with far-reaching, costly individual and public health effects, the specific causes of and solutions to the problem are less clear. Observational studies focusing on the factors that cause medication nonadherence have shown that it is a complex behavior with multiple determinants. Factors at the levels of *health policy*, *the health system*, *health care provider*, and *the patient* can lead to medication nonadherence or foster better adherence. Many studies have examined the multiple factors associated with medication adherence. Bosworth[32] classified these factors into the following categories: policy, health care systems, the social environment, individual provider characteristics, regimen characteristics, and patient characteristics.

Health policies not only support health care systems but also influence broader societal factors that affect the patient's ability to adhere, such as gaining access to health care and health insurance or paying for medical treatment. Health system factors that affect medication adherence include clinicians' behaviors and broader infrastructural features of a health system, such as communication systems for interdisciplinary teams that may contribute to better medication adherence. Thus, at the systems level, lack of access to a provider who will monitor the response to medication and change the dosage or medication type accordingly may negatively impact long-term adherence to medication regimens. Assuming a patient has access to a health care provider who prescribes an appropriate medication, at the correct dose, and for the correct duration, *health system and health provider* factors related to nonadherence include a wide array of potential problems—for instance, inadequate instructions given for taking the medication; insufficient labeling of the medication container to promote correct adherence; and inadequate information given about the benefits and risks of and alternatives to the prescribed medication. Many *health care systems* operate on an acute care model that fails to engage patients in their own care and is a barrier to promoting adherence to chronic illness treatment that requires such engagement.[15] Hence, understanding ways to overcome such barriers at the system level is particularly important in the setting of long-term treatment for chronic diseases.

Likewise, many *patient factors* underlie nonadherence. For example, patients may lack the cognitive ability to understand the need for the medication or how to take it. Others may not feel motivated to take the medication or may lack the skills and resources that support adherence.[45-47] Substance abuse, depression,[8, 45, 48, 49] lack of medical insurance, competing demands on time, and having an erratic daily routine can all impede optimal medication use.[18, 45] Moreover, the factors that most influence adherence differ across individuals.[45] Therefore, interventions to improve adherence are often multipronged and tailored. Of note, the cognitive barriers that patients with psychosis, mania, or bipolar disorder face in taking medication likely differ in material ways from those associated with other chronic conditions; for purposes of this review, we are excluding studies involving patients with psychosis, mania, and bipolar disorder.

In addition, patients may be nonadherent in many ways. For example, some patients may omit doses of a medication, whereas others may take extra doses. Also, they may take the wrong

amount of the medication—either too little or too much—or take the medication at the wrong time of day. Patients can also be nonadherent simply by not following instructions on how to take the medication (e.g., with or without food). Also, they may take drug holidays, whereby they discontinue the medication for a period of time or even discontinue the medication altogether.

Health and Health Care Disparities

Health and health care disparities exist for many common chronic diseases, including cardiovascular disease, diabetes mellitus, hypertension, HIV infection, and depression. However, the extent to which these differences can be attributed to medication adherence is unclear. Ethnic differences in medication-adherence rates may partly explain observed health disparities.[47, 50, 51] For example, multiple studies have documented that African-American patients are less adherent to antiretroviral treatment than white patients and have postulated that this phenomenon may explain differences in clinical outcomes.[46, 47, 50, 51] Although the reasons for these differences in adherence are not fully understood, phenomena such as less trust in the health care system have been suggested. Similarly, poor adherence has been identified as particularly problematic for older adults, who often must take multiple medications in the face of physical and cognitive limitations.[52]

Low health literacy may also be linked to poor adherence and poor health outcomes. Health literacy is defined in *Healthy People 2010* as the degree to which individuals can obtain, process, and understand the basic health information and services they need to make appropriate health decisions.[53] In a systematic review of 44 studies that examined the relationship between health literacy and health outcomes, 16 examined the association between health literacy and knowledge.[54] Health literacy was associated with greater knowledge in 14 of the 16 studies reviewed, including studies that examined patient knowledge of diabetes, hypertension, and heart health.[55, 56] Low literacy has also been associated with greater risk of hospitalization[57, 58] and poorer control of type 2 diabetes.[55, 59-61]

Only a handful of studies have examined the association between health literacy and medication adherence, however, and the results of these studies have been conflicting. Whereas Kalichman and colleagues found low health literacy to be associated with poorer compliance with highly active antiretroviral therapy among HIV-infected patients,[62] other studies have failed to replicate this finding.[45, 63] Nonetheless, other studies demonstrate that patients with low literacy skills have difficulty understanding prescription warning labels and identifying their medications correctly.[64, 65] A recently updated systematic review of health literacy also found insufficient evidence to identify a definitive link between low health literacy and medication adherence.[66, 67] This same review identified only two quasi-experimental trials of interventions to enhance adherence by addressing low health literacy.[68, 69] These two studies found no difference in the effect of their self-management interventions by health literacy level, although they reported insufficient information to determine overall or subgroup effect sizes.[66] Although patients with limited literacy skills may be at greater risk than others for medication misadministration, conclusive data about whether this is the case, and if so, how best to address the issue are not yet available.

Medication Adherence Improvement Strategies

This review seeks to synthesize evidence regarding the efficacy and effectiveness of interventions to improve adherence to medication regimens used to treat chronic illness among

adults. Although intervention labels and components vary greatly, we list below some common characteristics of interventions. These common characteristics of interventions may be less applicable for interventions that target policy levels.

- **Intervention Target**: The target refers to the person, people, health system, or policy to which intervention activities are directed. Although the ultimate goal of adherence interventions is to improve patient medication-taking behavior, interventions may do this by directly targeting providers, patients, aspects of a health system, health policies, or some combination of these four.
- **Intervention Agen**t: An intervention agent is the person, people, or technology used to deliver the intervention. Examples of possible intervention agents include physicians, nurses, pharmacists, case managers, multidisciplinary teams, or family members. Some interventions may have more than one agent delivering an intervention or a part of an intervention.
- **Mode of Delivery**: The mode of delivery refers to the manner by which the agent delivers the intervention. For example, interventions may be delivered face-to-face; over the telephone; using print materials; by computer; or on a DVD, video, or CD/audio. Like intervention target and agent, an intervention may have more than one mode of delivery.
- **Intensity of Intervention**: Medication adherence interventions also vary in their intensity or dose. Intensity refers to the total amount of time an intervention lasts, taking into account the duration and number of all individual sessions.
- **Duration of Intervention**: In contrast to intensity, the duration of an intervention is a description of the total length of calendar time over which the series of individual sessions are delivered. Two interventions may have the same total intensity (e.g., five 30-minute sessions) but be spread out over different total durations of time (e.g., one over 1 month, another over 1 year).
- **Components of Intervention**: DeBruin et al. developed a taxonomy of 16 mutually exclusive medication adherence intervention components that may or may not be present in an adherence intervention.[70] An intervention may include one or more of these components. Examples of these components include features such as knowledge-based activities, awareness-based pursuits, self-efficacy enhancement, and contingent rewards.

Practitioners developing and implementing medication adherence interventions may combine each of these key characteristics with various other characteristics to generate very diverse sets of interventions; these are most often compared only with a usual care program rather than with one another. Hence, this report had two important goals: (1) to identify features of interventions that clustered together into broader categories of intervention types and (2) to determine whether such intervention types exist across diseases or tend to cluster within diseases. For example, integrated care models are often used in settings dealing with chronic mental illness and generally are delivered by multidisciplinary teams; they target the health system by creating new structures by which clinicians may interact with one another to care for the patient. Such models may have common components that could be combined to address adherence among patients with other chronic illnesses.

The type and features of intervention studies may have important implications for the cost, feasibility, and scalability of the interventions tested. For example, face-to-face interventions may be more costly than other modes in general. As their intensity increases, and as the training level required of the delivery agent rises, their costs will likely rise and their feasibility will

likely drop. Nonetheless, greater intensity may be needed to achieve efficacy in improving adherence. Because intensity and other features of an intervention often covary, isolating the effects of one over another in the absence of a direct comparison is not possible.

In general, few harms are associated with the interventions being considered. Some studies have assessed patients' satisfaction with their health care and/or with their health care practitioner to ensure that the intervention does not interfere with ongoing relationships with a clinic or doctor. In addition, interventions that improve patients' medication taking might result in patients experiencing increased medication side effects if these patients were previously taking too little of their medication. Hence, some studies have assessed whether an adherence intervention led to any untoward medication side effects. Conversely, particularly for interventions that involve more interactions with health professionals, other benefits may occur that are not fully attributable to enhanced medication taking, such as improved quality of life or increases in perceived social support.

Thus, the causal pathways among such factors, the intervention, levels of medication adherence, and the attendant benefits and harms are complex, difficult to tease apart, and potentially circular. For example, an intervention may directly enhance quality of life through increased social support, but this improved quality of life may also be a mechanism that enhances medication adherence, which in turn further enhances health and quality of life. Few studies of adherence interventions are designed to distinguish such causal pathways.

Scope, Key Questions, and Analytic Framework

Scope of the Review

This report is part of a larger initiative, *Closing the Quality Gap: Revisiting the State of the Science* (CQG), which builds on the AHRQ 2004 to 2007 collection of publications—*Closing the Quality Gap: A Critical Analysis of Quality Improvement Strategies*—that summarized the evidence on quality improvement strategies for chronic conditions.[71] This new series continues to summarize evidence on means to improve quality of care, but it focuses on selected settings, interventions, and clinical conditions. Both series were launched in response to an IOM study, *Priority Areas for National Action: Transforming Health Care Quality*, that identified several gaps or discrepancies between medical treatment expected to be efficacious when optimal care is delivered based on known evidence and what actually happens across populations of patients.[72] Our report, one of eight in the second series, addresses the comparative effectiveness of adherence intervention strategies, one keystone to improving the gap between potential and realized quality health care.

To improve health care quality, interventions used to improve medication adherence have been developed that address *individual*, *health care provider*, or *health system* factors; some address factors on more than one level. In addition, a few studies have tried to assess the effect of broader *policy level changes* on medication adherence of individuals. Previous reviews demonstrate considerable variability across interventions in terms of both approach and effectiveness.[7, 73] In a recently published meta-analysis of 61 trials of individual-level programs to improve medication adherence,[19] the effect size for improved adherence in the behavioral cohorts (the only ones meeting homogeneity criteria) was 7 percent (95% confidence interval [CI], 4 to 9); for educational interventions, it was 11 percent (95% CI, 6 to 15); and for combined interventions, it was 8 percent (95% CI, 4 to 12). Although most adherence-intervention trials have demonstrated only modest improvement, a recent trial of a pharmacy care program reported

substantial improvement in adherence, suggesting that assessing not only individual but also health systems-level interventions is important.[74]

Questions about the types of programs most likely to be effective in various settings remain unanswered. For example, reviews of behavioral interventions have shown that those developed to address specific constructs based on a specific behavioral theory are more effective than those that were not;[75] however, this feature has not been compared for medication adherence[76] or across diseases. The last comprehensive review on this topic was a 2008 update of a Cochrane review.[28] It found that "several quite simple interventions increased adherence and improved patient outcomes, but the effects were inconsistent from study to study with less than half of studies showing benefits."[7(p. 2)] The authors, however, analyzed the results by clinical condition rather than by the type of intervention, vulnerable subpopulations, methods used to assess adherence, purpose of medication (primary, secondary, or tertiary prevention), or disease-specific measures (severity/stage of disease), all of which would provide more guidance for strategies to improve health care quality.

Patterns of adherence and factors influencing it have been shown to differ for acute disease when compared with chronic disease,[20] likely because of the longer duration of medication taking required with chronic disease. For this reason, and because their longer duration means that chronic diseases cause greater disease burden, our review focuses on adherence to medication for chronic illness; this will permit us to maintain comparability across intervention types. Moreover, the earlier Cochrane review and update did not assess the impact of system-level or policy-level interventions on adherence.[7] Thus, in our review, we will assess these interventions in addition to those at the patient and clinician levels. Because recent reviews and meta-analyses have assessed the impact of interventions to improve medication adherence in the context of HIV treatment,[76-78] we exclude antiretroviral adherence intervention studies from our review.

To address the issues outlined above, the overarching goal of our systematic review is to maximize the quality of care for adults with chronic disease. The means to this end are to identify *individual-, provider-, system-,* and *policy-level interventions* that have been shown to improve medication adherence, to clarify key components of effective interventions, and to document how intervention effectiveness varies for vulnerable subpopulations (such as racial and ethnic minorities, low–health literacy groups, the elderly, and so on). Moreover, because severe mental illness adds a layer of complexity to the cognitive features of medication adherence that make it less generalizable across other diseases, we did not include studies of medication adherence interventions for schizophrenia, bipolar disorder, or substance abuse. Moreover, we elected to focus our review on studies that sought specifically to assess intervention effects on medication adherence, regardless of whether they assessed additional health outcomes. In previous Cochrane reviews of adherence interventions,[28] studies were included only if they assessed health outcomes beyond medication adherence, such as mortality or morbidity measures. Although we recognize that an ultimate goal of improving medication adherence is to improve health outcomes, to go beyond the previous review and to avoid missing studies of interventions that may have had an effect on adherence behavior that could suggest mechanisms by which such interventions work, we included all eligible studies that assessed intervention effects on medication adherence. For those that had an effect on adherence and measured other health outcomes, we assessed the effects on those outcomes as well.

Key Questions

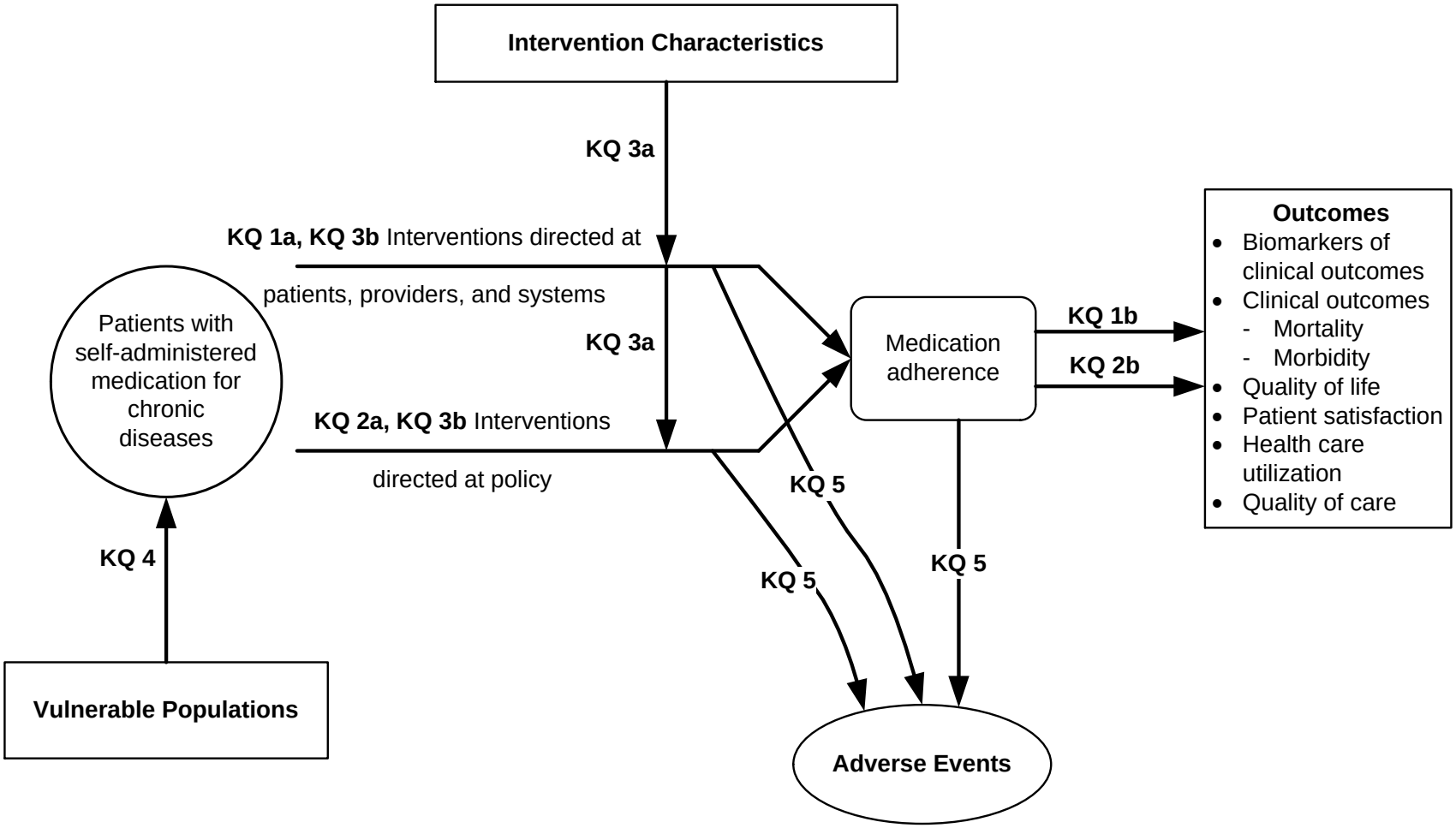
This report addresses five key questions (KQs), three of which have subquestions. Specifically, they are

- KQ 1a: Among patients with chronic diseases with self-administered medication prescribed by a provider, what is the comparative effectiveness of interventions aimed at patients, providers, systems, and combinations of audiences in improving medication adherence?
- KQ 1b: Is improved medication adherence associated with improvement in patient outcomes?
- KQ 2a: Among patients with chronic diseases with self-administered medication prescribed by a provider, what is the comparative effectiveness of policy interventions in improving medication adherence?
- KQ 2b: Is improved medication adherence associated with improvement in patient outcomes?
- KQ 3a: How do medication-adherence intervention characteristics (e.g., mode of delivery, intervention target, intensity) vary?
- KQ 3b: To what extent do the effects of adherence interventions vary based upon their characteristics?
- KQ 4: To what extent do the effects of adherence interventions vary based on differences in vulnerable populations?
- KQ 5: What unintended consequences are associated with interventions to improve medication adherence?

Analytic Framework

We developed an analytic framework to guide the systematic review process (Figure 1). Both KQ 1 and KQ 2 assess the comparative effectiveness of adherence interventions among our study populations. However, because researchers used unique study designs to test policy-level interventions studies, we elected to separate interventions aimed at nonpolicy targets (i.e. patient, provider, health system) (KQ 1) from those aimed at policy-level targets (KQ 2). Moreover, because we sought to go beyond other reviews by assessing all interventions targeting medication adherence (i.e., not limited to those that also assessed health outcomes), we split these two questions into their effects on adherence (KQ 1a; KQ 2a) and on other health outcomes (KQ 1b; KQ 2b). Because of the broad diversity of interventions and the paucity of studies that directly compared or isolated the effects of specific intervention features, in KQ 3 we first sought to describe, characterize, and quantify the features of interventions tested (KQ 3a) and then to determine the relationship between such characteristics and their effects (KQ 3b). To gain an understanding of intervention effects among specific populations identified by AHRQ and IOM as vulnerable, priority populations, we asked KQ 4. Finally, KQ 5 focuses on identifying adverse effects of interventions on health outcomes.

Figure 1. Draft analytic framework for medication adherence



Population, Intervention, Comparator, Outcomes, Timing, and Setting

We provide the following detailed description of relevant populations, interventions, comparators, outcomes, timing, and settings (PICOTS).

Populations

The primary populations of interest are community-dwelling adult patients who are prescribed self-administered medications for single or multiple chronic diseases. Vulnerable populations of interest may include (but are not limited to) racial and ethnic minorities; populations with special health care needs (such as low health literacy, comorbid disease, or severe illness); the elderly; and low-income, underinsured, uninsured, and inner-city or rural populations. Relevant medications include all prescribed medications, including over-the-counter drugs. The specific medications vary by clinical condition.

Interventions

As noted above, we have two categories of interventions.

- Any intervention intended to improve adherence with prescribed, self-administered medications. Examples include:
  - Patient education
  - Face-to-face or telephone counseling or therapy (individual, couple, family, or group)
  - Behavioral interventions
  - Case management
  - Simplified dosing
  - Reminders
  - System changes
  - Changes to medication formulations (e.g., oral versus subcutaneous)
  - Augmented pharmacy services
  - Shared decisionmaking
  - Dose-dispensing units of medication or medication charts
  - Rewards
- Any intervention intended to address policy barriers. Examples include changes in insurance copay and refill practices (e.g., how long medications are prescribed for, how often patients have to order refills) and changes in formularies.
- Characteristics of the intervention that may influence effectiveness include but are not limited to the following:
  - Target of the intervention
  - Agent delivering the intervention (e.g., physician, nurse, or health educator) and his/her characteristics/level of training
  - Intensity (contact time)
  - Duration (number of sessions over a given time period)
  - Delivery mode (e.g., face-to-face, written material, text message, computer, phone)
  - Role of theory
  - Number of components
  - Type of components (based on the taxonomy proposed by de Bruin and colleagues[70]):

- Knowledge-based (general information about behavior-related health consequences, use of individualized information, increase in understanding/memory enhancement)
- Awareness-based (risk communication, self-monitoring, reflective listening, behavioral feedback)
- Social influence (information about peers or social influence of peers)
- Attitude-based
- Self-efficacy (modeling, practice, verbal persuasion, coping responses, graded tasks, reattribution of success/failure)
- Intention formation (general intention, medication schedule, goals, behavioral contract)
- Action control (cues/reminders, self-persuasion, social support)
- Maintenance (maintenance goals, relapse prevention)
- Facilitation (continuous professional support, dealing with adverse effects, individualizing/simplifying regimen [fewer pills, fewer medications, less frequent dosing, timing of dosing to fit individual schedule], reducing environmental barriers)
- Contingent rewards
- Motivational interviewing
- Stress management

Comparators

These can be either (1) usual or routine care, defined as the absence of an intervention to improve medication adherence or (2) some type of active intervention intended to improve medication adherence.

Outcome Measures

We will examine three types of outcomes:

- Medication adherence
- Other outcomes
  - Biomarkers of clinical outcomes
  - Clinical outcomes (mortality, morbidity measures defined by the clinical condition)
  - Quality of life
  - Patient satisfaction
  - Health care utilization (including associated costs), and
  - Quality of care
- Adverse events

Timing

We consider all possible lengths of interventions and follow-up periods.

Setting

Outpatient primary and specialty care settings are included. Institutional settings such as inpatient care, nursing homes, and prisons are excluded. Studies conducted outside the United States are excluded; studies conducted in other settings may be of limited applicability in the United States.

Organization of This Report

The remainder of this review describes our methods in detail, documents our results, and provides a discussion of our findings and recommendations for filling important research gaps. Appendixes provide details of the search strategy (Appendix A), forms used for review and abstraction (Appendix B), studies excluded at the full-text review stage (Appendix C), comprehensive evidence tables (Appendix D), risk of bias ratings (Appendix E), a list of scales and abbreviations used in included studies (Appendix F), and a summary of strength of evidence grades for KQ 1 (Appendix G).

Methods

The methods for this review follow the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews (available at http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm). The main sections in this chapter reflect the elements of the protocol established for the review (and the Closing the Quality Gap series). All methods and analyses were determined a priori, unless otherwise specified.

Topic Refinement and Review Protocol

Topics for the Closing the Quality Gap series were solicited from the portfolio leads at AHRQ. The nominations included a brief background and context; the importance and/or rationale for the topic; the focus or population of interest; relevant outcomes; and references to recent or ongoing work. Among the topics that were nominated, the following considerations were made in selection for inclusion in the series: the ability to focus and clarify the topic area appropriately; relevance to quality improvement and a systems approach; applicability to the EPC program/amenable to systematic review; the potential for duplication and/or overlap with other known or ongoing work; relevance and potential impact in improving care; and fit of the topics as a whole in reflecting the AHRQ portfolios.

The EPC then worked on clarifying the scope of the project. A key consideration was ensuring that the report built upon and added to existing syntheses of this topic. Rather than replicate ongoing updates of a Cochrane review by Haynes and colleagues,[28] we sought to address some of the areas outside its purview, and in doing so, pay attention to the themes of the Closing the Quality Gap series and AHRQ's concerns regarding priority and vulnerable populations. The specific constraints of the Haynes review that we wanted to address included (1) the requirement that both adherence and health outcomes are reported in a study, (2) the focus on randomized controlled trials alone, (3) the absence of subanalyses on vulnerable subpopulations, and (4) the lack of focus on adverse events and cost-effectiveness.

As noted in the introduction, one reason for expanding the scope to include studies that report adherence alone rather than both health outcomes and adherence is that this approach allowed us to include a more representative range of interventions that might improve adherence. We note that interventions may be designed to alter moderators of medication adherence at the level of the patient, health care provider, health system, or policy. The reason for expanding the scope to include some observational studies (such as controlled clinical trials, cohort studies with comparators, and large database analyses) is that these studies allowed us to assess the effectiveness of policy innovation in practice settings that are not usually tested in trial settings.

AHRQ staff generated the initial topics for this series and our review. We generated an analytic framework, preliminary Key Questions (KQs), and preliminary inclusion/exclusion criteria in the form of PICOTS (populations, interventions, comparators, outcomes, settings). Our KQs were posted for public comment on AHRQ's Effective Health Care Web site from March 11, 2011, to April 8, 2011. We revised the KQs as needed based on review of the comments and discussion with a five-member Technical Expert Panel (TEP), primarily for readability and greater comprehensiveness.

TEP members represented several professions (medicine, nursing, and pharmacy) and research areas (health services, pharmacoepidemiology, patient education, self-management, and

health literacy). They provided high-level content and methodologic expertise throughout the development of the review.

Literature Search Strategy

Search Strategy

To identify articles relevant to each KQ , we began with a focused MEDLINE® search for medication adherence interventions using a combination of Medical Subject Headings (MeSH) and title and abstract keywords (Appendix A). We searched Cochrane Library and the Cochrane Central Trials Registry using analogous search terms. To identify articles specifically relevant to KQ 2, we conducted a second, "policy-oriented" search (Appendix A) and added unique results to those references identified in the main search for medication adherence interventions. We reviewed our search strategy with the TEP and supplemented it as needed according to their recommendations. In addition, to avoid retrieval bias, we manually searched the reference lists of pertinent reviews on this topic to look for any relevant citations that might have been missed by our searches. We imported all citations into an EndNote® X4 (Thomson Reuters, New York, NY) electronic database.

We will also conduct an updated literature search (of the same databases searched initially) concurrent with the peer review process. Any literature suggested by peer reviewers or from the public will be investigated and, if appropriate, incorporated into the final review. Appropriateness for inclusion in the review will be determined by the same methods listed above.

Inclusion and Exclusion Criteria

Table 2 presents the inclusion/exclusion criteria for our review. Details about PICOTS related to inclusion/exclusion criteria can be found in the Introduction chapter.

Table 2. Inclusion/exclusion criteria

	Criteria	
Category	**Inclusion**	**Exclusion**
Population	• Adults prescribed self-administered medication for secondary or tertiary prevention of chronic diseases	• Children under the age of 18 (no adults in the study or outcome of interest not stratified by child/adult) • Patients administered medications in hospitals or in offices • Patients undergoing primary prevention • Patients taking over-the-counter medicines not prescribed by a provider • Patients with infectious conditions (e.g., HIV/AIDS, tuberculosis, pelvic inflammatory disease) • Patients with mental illness involving psychosis, mania, or bipolar disorder • Patients on medication to treat substance abuse
Geography	• United States	• All non-United States
Time period	• 1994 to present; searches to be updated after draft report goes out for peer review	• Pre-1994
Length of followup	• No limit	

Table 2. Inclusion/exclusion criteria (continued)

Category	Criteria	
	Inclusion	Exclusion
Settings	• Outpatient primary and specialty care settings • Community-based • Home-based	• Institutional settings (e.g., inpatient care, nursing homes, prisons)
Interventions	• Any intervention for included clinical conditions intended to improve adherence with prescribed, self-administered medications	• Interventions intended to improve compliance with primary prevention measures (e.g., screening, diet, exercise, lifestyle changes)
Outcomes	• Medication adherence • Biomarkers, mortality, morbidity, quality of life, patient satisfaction, healthcare utilization (and associated costs), quality of care for studies with a statistically significant improvement in medication adherence • Adverse events	
Publication language	• English	• All other languages

Admissible evidence for KQ 1 on patient-level, provider-level, or systems-level interventions (study design and other criteria)	• Original research; eligible study designs include:
	  ○ Randomized controlled trials
	  ○ Systematic reviews with or without meta-analyses
		• Nonrandomized controlled trials
		• Observational study designs
		• Case series
		• Case reports
		• Nonsystematic reviews
		• Editorials
		• Letters to the editor
		• Articles rated high risk of bias
		• Studies with historical, rather than concurrent, control groups
		• N<40

Admissible evidence for policy-level interventions (study design and other criteria)	• Original research; eligible study designs include:
	  ○ Randomized controlled trials
	  ○ Systematic reviews with or without meta-analyses
	  ○ Nonrandomized controlled trials
	  ○ Cohort studies
	  ○ Case-control studies
	  ○ Time series
	  ○ Before-after studies
		• Cross-sectional studies
		• Case series
		• Case reports
		• Nonsystematic reviews
		• Editorials
		• Letters to the editor
		• Articles rated high risk of bias
		• N<40

Study Selection

Two trained members of the research team independently reviewed all titles and abstracts (identified through searches) for eligibility against our inclusion/exclusion criteria. The abstract review form is shown in Appendix B. Studies marked for possible inclusion by either reviewer underwent a full-text review. For studies that lacked adequate information to determine inclusion or exclusion, we retrieved the full text and then made the determination. All results were tracked in an EndNote® database.

We retrieved and reviewed the full text of all titles included during the title and abstract review phase. Two trained members of the team independently reviewed each full-text article for

inclusion or exclusion based on the eligibility criteria described above. The full-text review form is shown in Appendix B. If both reviewers agreed that a study did not meet the eligibility criteria, the study was excluded. If the reviewers disagreed, they resolved conflicts by discussion and consensus or by consulting a third member of the review team. All results were tracked in an EndNote database. We recorded the principal reason that each excluded full-text publication did not satisfy the eligibility criteria (Appendix C).

Data Extraction

For studies that met our inclusion criteria, a trained reviewer abstracted important information into evidence tables; a second senior member of the team reviewed all data abstractions for completeness and accuracy. We designed and used structured data abstraction forms to gather pertinent information from each article, including characteristics of study populations, settings, interventions, comparators, study designs, methods, and results. All data abstraction was performed using Microsoft Excel® software. Evidence tables containing all abstracted data from included studies are presented in Appendix D. Evidence tables are presented in alphabetical order by last name of first author. A list of scales used in included studies is presented in Appendix F.

As implied by KQ 1 and KQ 2, we abstracted data on other outcomes only for interventions that showed statistically significant improvement in at least one measure of medication adherence. We used thresholds for medication adherence as defined by each study, that is, we did not predefine standards for improvement in medication adherence for all clinical conditions. We recorded all morbidity and biomarker data for studies reporting any statistically significant improvement in medication adherence. We abstracted information on patient characteristics such as age, sex, race and ethnicity, special health care needs (such as low health literacy, comorbid disease, or severe disease), income, insurance status, and geographic location (inner city or rural), when available. We recorded intention-to-treat (ITT) results when available. We also abstracted intervention characteristics as described in KQ 3.

Risk of Bias Assessment of Individual Studies

To assess the risk of bias (internal validity) of studies, we used predefined criteria based on those developed by AHRQ[79] and specified in the RTI Item Bank.[80] We used specific questions from a validated instrument. In general terms, the results from a low-risk-of-bias study are considered to be valid. A study with moderate risk of bias is susceptible to some risk of bias but probably not enough to invalidate its results. A study assessed as high risk of bias has significant risk of bias (e.g., stemming from serious errors in design or analysis) that may invalidate its results.

Specific concerns for our review include selection bias, information bias, and detection bias. For selection bias, we evaluated studies for their approaches to sampling and accounting or controlling for variations in past nonadherent behavior. We also evaluated whether the intervention measured or accounted for any skills necessary for patients to be adherent to medication regimens. For information bias, we evaluated studies for their application of proper research design to reduce the possibility that factors other than the interventions affected outcomes of interest. Design elements that reduced the risk of information bias included the use of double blinding, allocation concealment, ITT analysis, nonselective outcome reporting, and strategies to prevent or reduce treatment contamination. When investigators did not use ITT

analysis, we considered the risk of information bias to be elevated if treatment completers differed from noncompleters or if completers were not compared with noncompleters.

For detection bias, we evaluated the method of recording adherence by using such strategies as determining whether adherence measures relied on self-report data. In addition, we assessed the construct validity of measures by reviewing any literature cited by study authors to justify their chosen measures.

Two reviewers independently assigned risk of bias ratings for each study. Disagreements between the two reviewers were resolved by discussion and consensus or by consulting a third member of the team. We excluded studies that were dually assessed as having high risk of bias from further analysis. The evidence tables present consensus ratings (Appendix E).

Data Synthesis

KQs 1, 2, 4, and 5 present results categorized by clinical condition. KQ 3 presents results categorized by intervention characteristics. We specified all nonmorbidity data a priori and listed them above in the PICOTS criteria. Because of the breadth of the topic for our review, we elected, based on feedback from our TEP, to collect a comprehensive set of biomarkers and morbidity outcomes rather than make a priori judgments about which specific outcomes to include. When appropriate data were available, we described results from direct comparisons. We did not attempt indirect comparisons, given the heterogeneity of usual care comparators.

We evaluated whether the collected data could be pooled by considering similarity of PICOTs. In instances with three or more similar studies (population, intervention, comparator, outcome), we considered conducting quantitative analyses (i.e., meta-analysis) of the data from those studies.

When quantitative analyses were not appropriate (e.g., because of heterogeneity, insufficient numbers of similar studies, or insufficiency or variation in outcome reporting), we synthesized the data qualitatively. We anticipated a high degree of heterogeneity in this literature that would generally preclude quantitative syntheses, and our review of PICOTs confirmed our initial assessment.

We intended to stratify our analyses and perform subgroup analyses when possible and appropriate in KQ 3. Planned stratifications or categories for subgroup analyses included disease type, intervention characteristics, racial and ethnic minorities, low-health-literacy groups, and the elderly.

Grading Strength of Evidence

We graded the strength of evidence based on the guidance established for the Evidence-based Practice Center program.[81] Developed to grade the overall strength of a body of evidence, this approach incorporates four key domains: risk of bias (including study design and aggregate quality), consistency, directness, and precision of the evidence. We also considered plausible confounding for KQ 2, which included observational studies.

We graded the strength of evidence for medication adherence, morbidity, mortality, and other long-term health outcomes for KQ 1 and KQ 2, for vulnerable subpopulations (KQ 4), and for harms (KQ 5). Two reviewers independently scored each domain for each key outcome and resolved differences by consensus; when they could not reach consensus, a third senior reviewer arbitrated the decision. Table 3 defines the strength of evidence grades. A summary of strength of evidence grades for KQ 1 is listed in Appendix G.

Table 3. Definitions of the grades of overall strength of evidence

Grade	Definition
High	**High confidence that the evidence reflects the true effect.** Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	**Moderate confidence that the evidence reflects the true effect.** Further research may change our confidence in the estimate of the effect and may change the estimate.
Low	**Low confidence that the evidence reflects the true effect.** Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	**Evidence either is unavailable or does not permit estimation of an effect.**

Source: Owens et al.[81]

Applicability Assessment

We assessed the applicability of the evidence following guidance from Atkins and colleagues.[82]

We used the PICOTS framework to explore factors that affect or limit applicability. They included the following:

- Population
  - Narrow eligibility criteria or exclusion of patients with comorbidities.
  - Large differences between demographics of the study population and community patients.
  - Narrow or unrepresentative disease severity, stage of illness, or comorbidities.
- Interventions
  - Intensity and delivery of behavioral interventions that may not be feasible for routine use.
  - Highly selected intervention team or level of training and proficiency not widely available.
- Outcomes
  - Composite outcomes that mix outcomes of different clinical or policy significance.
  - Short-term or surrogate outcomes.

Peer Review and Public Commentary

[This section will be updated for the final report once the review has been completed.]

Results

Introduction

This section presents the results of the literature searches, followed by results for each key question (KQ). KQ 1 presents evidence on medication adherence and other outcomes for patient, provider, and systems interventions. KQ 2 presents similar evidence for policy interventions. No overlap exists between these two bodies of evidence. KQ 3 (on intervention characteristics and direct comparisons of intervention components [KQ 3b]), KQ 4 (on vulnerable populations), and KQ 5 (on adverse effects) are cross-cutting questions that draw upon available evidence from KQ 1 and KQ 2.

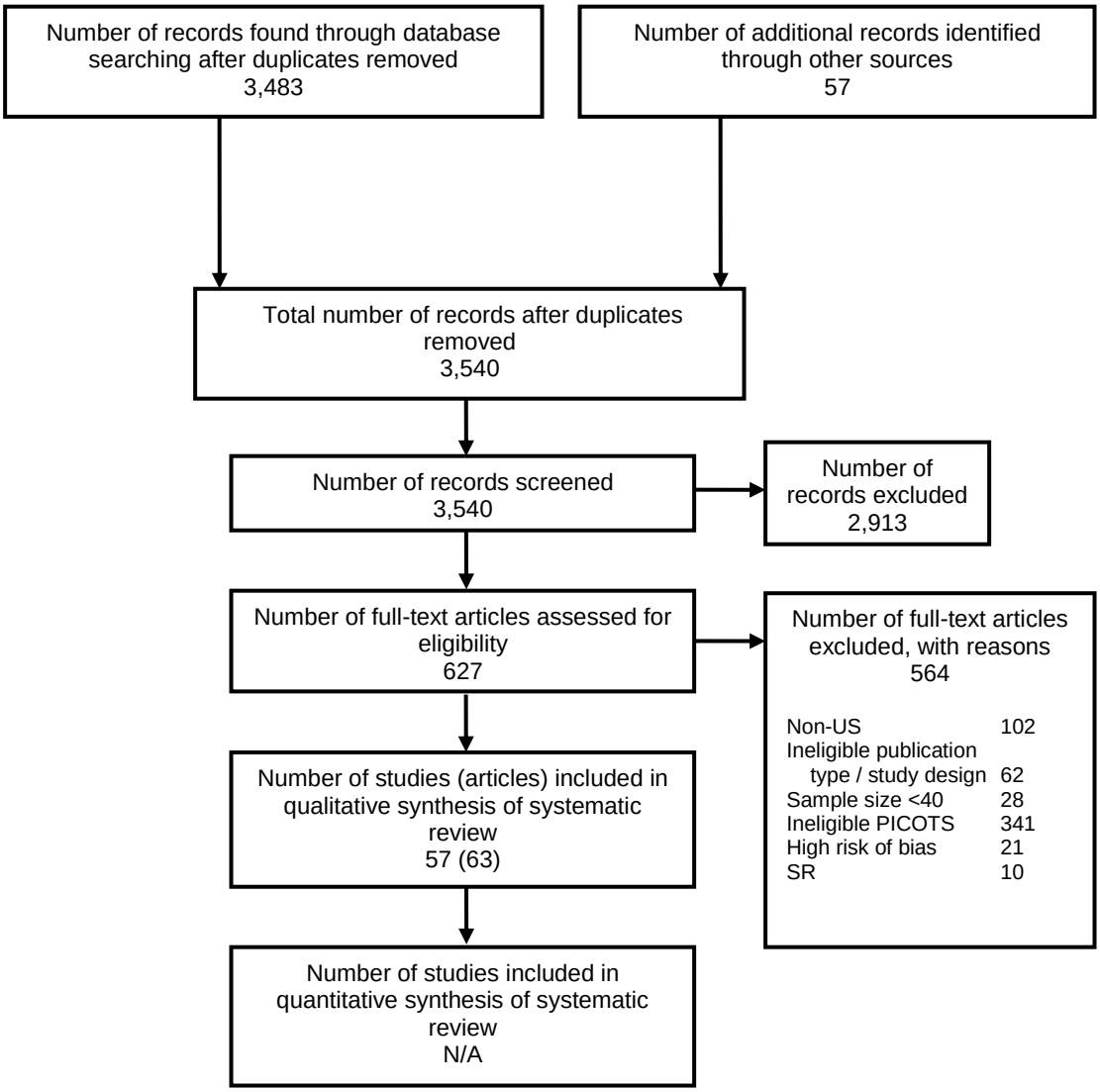
Results of Literature Searches

Figure 2 presents our literature search results. Literature searches through April 25, 2011, for the current report identified 3,483 unduplicated citations. Handsearches of systematic reviews and other sources added a total of 57 additional citations. All of these sources produced a total of 3,540 references.

After applying our eligibility and exclusion criteria to titles and abstracts of all identified citations, we obtained full-text copies of 627 published articles. We reapplied our inclusion criteria and excluded 543 of these articles from further review. Twenty-one articles were not included because of a high risk of bias. We included a total of 63 articles for qualitative synthesis. Appendix C provides a list of excluded studies and reasons for exclusion at the full-text stage. Evidence tables for the 63 articles included for qualitative synthesis can be found in Appendix D; risk of bias assessments for the 84 articles included after full-text review can be found in Appendix E.

The 63 articles included in this review represent 57 studies. Of the 63 included articles, 60 were randomized controlled trials, and 3 were observational studies. Among the trials, 49 used a parallel randomization scheme, while 11 used cluster randomization. Fifty-four of the included articles were assessed as medium risk of bias, and 9 met the standards for low risk of bias.

Figure 2. Disposition of articles (PRISMA figure)



Abbreviations: PICOTS, population, intervention, comparator, outcomes, timing, setting and study duration; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SR, systematic review

Key Question 1. Patient, Provider, and Systems Interventions

Descriptions of Included Studies

We found 54 studies (comprising 60 articles) that address patient, provider, systems, or combinations of these targets in addressing medication adherence and other outcomes. As noted earlier, this key question is organized by the clinical condition for which we found evidence: diabetes; hyperlipidemia; cardiovascular conditions, specifically hypertension, heart failure, and myocardial infarction; reactive airways diseases, specifically asthma and chronic obstructive

pulmonary disease; depression; glaucoma; multiple sclerosis; musculoskeletal disorders; and multiple or unknown chronic conditions. KQ 1 presents an integrated discussion of medication adherence (KQ 1a) and other outcomes (KQ 1b) for greater ease of interpreting the effect of each intervention within a clinical area.

We elected to use descriptors of interventions based on common features and terminology specific to each clinical condition rather than impose an external taxonomy of our making for two reasons. First, the primary organizational principle for this KQ is by clinical condition: using terminology specific to each clinical condition maintains and supports this organizational structure. Second, because no overarching taxonomy of intervention types exists that will apply across medication adherence interventions for all chronic conditions, we believe an inductive approach is more appropriate. As a result, we note that intervention characteristics with similar features across clinical conditions may have different names. For instance, "care coordination" in diabetes may have many features in common with "collaborative care" for depression. We list the clinical conditions and interventions clusters in Table 4. These intervention descriptors generally reflect the target of the intervention and/or the agent of the intervention.

The remainder of this section describes the characteristics of studies, key points, and a detailed synthesis for each clinical condition in the order listed in Table 4. We support the analysis for each clinical condition by tables describing the characteristics of the study, medication adherence outcomes (other outcomes when available), and strength of evidence tables for each intervention type. We present the study characteristics table within the section on characteristics of studies, and list all medication adherence, other outcomes, and strength of evidence tables at the end of the detailed synthesis sections. Tables for study characteristics, medication adherence outcomes, and other outcomes are listed in order of last name of the first author of the study.

For each section on characteristics of the study, we present an overview, followed by details on population, intervention, comparator, outcome and timing, setting, and applicability. The key points sections in this report make a distinction between "insufficient" grades for bodies of evidence in which some research exists on the outcomes but is insufficient to make a call on the strength and bodies of evidence in which no research exists. As noted in the Introduction and Methods sections, we synthesize evidence on other outcomes only for studies that have demonstrated a statistically significant difference in medication adherence outcomes. As a result, strength-of-evidence grades of insufficient or low for other outcomes reflect the paucity of the evidence on these outcomes based on the subset of studies that demonstrate improvement in medication adherence. Strength-of-evidence grades for other outcomes cannot and should not, for example, be interpreted as evidence of effectiveness of improvement of multicomponent intervention strategies that may alter health outcomes through mechanisms other than medication adherence.

Table 4. Number of included studies by clinical condition, intervention, comparator, and outcome

Clinical Condition	Intervention	Comparator	Number of Studies
Diabetes[83-85]	Care coordination and collaborative care	Usual care	3
Diabetes[86-88]	Decision aids	Educational interventions	2
Diabetes[89]	Health coaching	Usual care	1
Diabetes[90]	Social support	Educational interventions	1
Hyperlipidemia[91-93]	Telephone-based interventions (e.g., reminders, active problem management, tailored support)	Usual care or less intense intervention	3
Hyperlipidemia[92, 94, 95]	Mail-based education (e.g., standard videos, tailored print)	Usual care	2
Hyperlipidemia[96]	Collaborative care	Usual care	1
Hyperlipidemia[86-88]	Statin decision aids	Educational interventions	2
Hyperlipidemia[74]	Pharmacist-led multicomponent (for 12 months)	Pharmacist intervention (for 6 months)	1
Hypertension[97-102]	Telephone-based education	Usual care	5
Hypertension[74, 103-107]	Pharmacist-led intervention (e.g., education, collaborative care, clinic)	Usual care or less intense intervention	5
Hypertension[95, 108]	Mail-based education (e.g., standard videos, tailored print)	Usual care	2
Hypertension[83, 90, 109]	Other interventions (e.g., collaborative care, nurse support, blister packing)	Usual care	3
Congestive heart failure[110]	Video and telephone reminders	Usual care	1
Congestive heart failure[111]	Pharmacist-led multicomponent	Usual care	1
Congestive heart failure[112]	Multi-setting, multidisciplinary	Usual care	1
Congestive heart failure[113]	Patient access to medical records and messaging system	Usual care	1
Myocardial infarction[114]	Mail-based communication to patients and providers about importance of medication adherence	Usual care	1
Asthma[115-119]	Self-management	Usual care	5
Asthma[120, 121]	Pharmacist or physician access to patient adherence information	Usual care or pharmacist training	2
Asthma[122]	Shared decisionmaking	Clinician decisionmaking or usual care	1
Depression[123, 124]	Telemonitoring	Usual care	2
Depression[84, 97, 125-127]	Case management	Usual care	3
Depression[83, 128-133]	Collaborative care	Usual care	6
Depression[134]	Reminder letters to nonadherent patients and monthly lists of nonadherent patients to providers	Usual care	1
Glaucoma[135]	Multicomponent	Usual care	1
Multiple sclerosis[136]	Software-based telephone counseling	Usual care	1
Musculoskeletal diseases[137, 138]	Case management	Usual care	2
Multiple or unspecified chronic conditions[139-141]	Pharmacist-based outreach, education, and problem solving	Usual care	3
Multiple or unspecified chronic conditions[142]	Case management	Usual care	1

Key Question 1. Diabetes: Medication Adherence Interventions

Description of Included Studies

Overview

We found eight articles reporting on seven randomized trials that assessed the effects of six different interventions aimed at improving medication adherence among adult patients with diabetes mellitus.[83-90] Six studies had a medium risk of bias[83, 85-90] and one study[84] had a low risk of bias. Table 5 presents an overview of the interventions. Table 6 through Table 9 present results for medication adherence and other outcomes for all studies, followed by strength of evidence tables by type of intervention (Table 10 through Table 13).

Population

Four studies reported limiting the sample to patients with type 2 diabetes or who were on oral hypoglycemic agents.[85-87, 89, 90] Two studies required a codiagnosis of depression[83, 84] and one a codiagnosis of uncontrolled hypertension.[90]

Interventions

Interventions varied widely in their approaches to improving adherence, although all were directed at patients (Table 5). Three of these studies[83-85] additionally targeted the health system and one of these also targeted providers.[85] Two studies that targeted patients only[86-88] tested a decision aid aimed at cardiovascular risk reduction choices; a third patient-only study that also focused on cardiovascular risk reduction provided education involving a social support person.[90] Two interventions used what the authors termed integrative approaches to disease management, each of which involved personalization of care;[84, 89] one used integrative health coaching and the other used an integrated care model delivered by a care manager. Although both of these studies reported using "integrative" approaches, in one, the care manager integrated the care the person was receiving—hence targeted both the patient and the system[84]—while the other entailed helping individuals to integrate their values with their own health behaviors and, hence, targeted only patients.[89] In one intervention, which was pharmacist-delivered,[85] pharmacists assessed patients' adherence barriers, provided tailored verbal patient education, and communicated these to physicians and social service providers. Finally, one study attempted to improve adherence to diabetes treatment by individualizing depression management using collaborative care;[83] which also required systems integration.

Taken together, the seven intervention studies described above fell into four clusters of intervention types. One cluster involved "care coordination" or "collaborative care" models, in the sense that, regardless of the agent delivering it, the intervention was designed to enhance health care by integrating different aspects of the care with one another. Means of integrating the care included enhancing communication between different provider types (e.g., between physicians and pharmacists[85] or between different subspecialists of physicians[83]) or using a care manager as a liaison between patient and physician.[84] This type of intervention addressed factors resulting in nonadherence and used a tailored individualized approach in which participants work with the intervention agent to develop strategies to overcome barriers to medication adherence. A second intervention type included decision aids.[86-88] These aids were designed to help patients with diabetes weigh the risks and benefits of taking a statin medication to reduce their risk of cardiovascular disease, given their individual baseline risk. Researchers postulated that

individuals who choose to take statins and are involved in that choice will be more likely to adhere to the medication because of that involvement. Two other studies were conducted, one for the "health coaching"[89] intervention and one for the "social support person"[90] intervention.

Comparator

Most studies compared an active arm to what was termed "standard of care" or "usual care" although their content was often not specified and, when it was, it varied among studies. In studies of decision aids, control participants were given an educational pamphlet containing standard of care information specified in one study as an American Diabetes Association pamphlet.[86-88] In the study seeking to enhance diabetes adherence by improving depression management, usual care was treatment of depression by the primary care physician.[83] In the study in which intervention participants received education while involving a social support person, the comparator was receipt of the same educational information without the involvement of a social support person.[90] Similarly, for the pharmacist-delivered intervention that was tailored to assess patient adherence barriers, those in the comparison group answered the same pharmacist-delivered barrier assessment questions but received no tailored strategies.[85]

Outcome and Timing

Adherence to diabetes medications was defined and assessed in a wide variety of ways; only two studies used a nonself-reported measure. The study that used Medication Event Monitoring System (MEMS) defined adherence as the percentage of participants taking more than 80 percent of their prescribed doses. The study using pharmacy refill data defined adherence as the percentage of time that prescriptions were filled on time. Among the five studies of self-reported adherence only, three studies[88-90] used the Morisky Adherence Scale although each defined adherence differently. Three used single items to ask about patients' medication taking, using a 7-day recall period,[85, 86, 89] but each defined adherence slightly differently—one as the number of <u>days</u> that <u>no</u> doses were missed,[85] one as the number of <u>people</u> who missed <u>no</u> doses,[86] and one as the <u>proportion of people</u> who missed <u>at least one</u> dose.[89] Some studies assessed adherence to nondiabetes medications, such as antidepressants, antihypertensives, and lipid-lowering agents. Only two studies[86-88] assessed the effects of the intervention on patients' initiation of treatment, and one of them[86, 87] also assessed persistence of medication taking (defined as the proportion of patients still on treatment at followup).

All of the studies, except the two testing decision aids, evaluated the effect of the intervention on HbA1C (glycosylated hemoglobin) levels. Other outcomes of interest included blood pressure and cholesterol levels, depression symptoms, body mass index, health-related quality of life, and patient satisfaction measures.

Timing and frequency of the study outcomes assessments also varied widely, ranging from 6 weeks to 12 months followup and from one to four times (every 3 to 6 months), respectively, as did the timing of the outcome assessment relative to administration or completion of the intervention.

Setting

Four studies were conducted in primary care settings;[83, 84, 88, 90] one was performed in a metabolic specialty clinic,[86, 87] one in an outpatient tertiary care center clinic,[89] and one in an academically-affiliated community health center.[85]

Applicability

The variety of settings in which these studies were conducted contributed to the overall applicability of the results. However, no studies assessed results among subgroups of patients with poorly controlled diabetes, limiting the applicability of the results to this population.

Key Points

Overview

- All seven studies assessed intervention effects on medication adherence (e.g., percentage of participants achieving a threshold of pills taken, proportion of pills taken, etc.) albeit each used a slightly different definition of medication adherence and tested different interventions. Overall, two of the seven[84, 86] demonstrated a statistically significant and large effect of the intervention on medication adherence. Although the interventions in each of these two studies were different types (a decision aid versus health coaching), both were delivered over relatively short time frames.

Care Coordination or Collaborative Care

- Medication adherence: Care coordination or collaborative care interventions improve medication adherence among patients with diabetes, particularly those with comorbid depression (low strength of evidence).
- Biomarkers of clinical outcomes: Care coordination or collaborative care interventions that resulted in better adherence improved HbA1C (low strength of evidence).
- Clinical outcomes: Care coordination or collaborative care interventions to improve adherence to depression and diabetes medications among patients with diabetes can lead to a clinically meaningful reduction in depressive symptoms (low strength of evidence).

Statin Decision Aid

- Medication adherence: We found inconsistent and imprecise results for the effect of decision aid interventions on medication adherence or initiation among patients with diabetes (insufficient strength of evidence).
- Patient satisfaction: Decision aid interventions improve patient satisfaction with some aspect of their care (low strength of evidence).

Health Coaching

- Medication adherence: One study showed no statistically significant differences in medication adherence between health coaching and usual care arms (insufficient).

Social Support

- Medication adherence: We found insufficient evidence to support the hypothesis that involving a social support person in a patient's diabetes education improves the patient's medication adherence (insufficient).

Other Outcomes for Care Coordination or Collaborative Care, Health Coaching, Social Support, and Decision Aids

- All other outcomes for the interventions listed above: Evidence was insufficient due to lack of data.

Detailed Synthesis for Care Coordination or Collaborative Care Interventions for Diabetes

Medication Adherence

Of three studies testing the effects of coordinating care models on medication adherence;[83-85] one, determined to have a low risk of bias, found an effect on adherence to both oral hypoglycemic agents and antidepressants at 6 weeks followup[84] and the other two, which both had a medium risk of bias, found no beneficial effect at 12[83] and 3 months,[85] respectively (Table 6).

The first of these three studies[84] assessed the effect of an integrated care manager intervention delivered to type 2 diabetic patients with depression over 4 weeks (three 30-minute in-person and two 15-minute telephone contacts in 4 weeks) on adherence to diabetes and antidepressant medications at 6 weeks followup, using MEMS. Data from this study showed large and statistically significant differences in adherence between intervention and control groups for both medications.

In the second care coordination study,[83] which tested a 1-year intervention of collaborative depression treatment, adherence to diabetes, blood pressure, and lipid-lowering medications (defined as the percentage of days of nonadherence based on 12-month pharmacy refill data) was not improved among intervention compared with control participants. Similarly, the intervention using a one-time pharmacist-administered phone session that included a questionnaire assessing barriers to adherence with tailored verbal education, physician feedback, and social service referrals found no differences from baseline to 3-month followup in self-reported adherence.[85] Taken together, these studies provide low strength of evidence that coordinating care model interventions improve medication adherence (Table 10).

Other Outcomes

HbA1C is sometimes considered a surrogate marker for adherence; however, because effects of HbA1c are considered to result from adherence, we present this outcome only for those studies that[84] demonstrated an effect of the interventions on adherence and presented results for HbA1c (Table 7). Of the four studies that assessed HbA1C as an outcome measure, only one study that tested a coordinating care model found the intervention to have an impact on adherence. Of note, this study also showed a statistically significant improvement in HbA1c among intervention group members at followup compared with controls. Taking the coordinating care model studies together, there is a low level of evidence that coordinating care interventions improve HgbA1c. The other study that found an effect on adherence[86, 87] did not assess HbA1C.

One study demonstrated a statistically and clinically significant impact of coordinating care intervention on symptoms of depression (Table 8).[84] The mean score on the Center for Epidemiologic Studies Depression Scale (CES-D) among patients in the intervention arm dropped from near the threshold for depression to well below it, whereas those in the control arm stayed above this threshold. There is low strength of evidence that this approach has a clinically

meaningful effect on depressive symptoms among patients with depression and diabetes mellitus (Table 8).

Detailed Synthesis for Decision Aid Interventions for Diabetes

Medication Adherence

The two studies of a decision aid[86-88] assessed its effects on both initiation of treatment among those not yet taking medication and adherence to the dosing regimen for those on treatment; one study assessed persistence with treatment over time (Table 10). The decision aid in both studies aimed to help diabetic patients decide whether or not to start or continue taking a statin to reduce their cardiovascular risk based on their individualized risks and benefits of taking statins tailored to their profiles. Both studies had relatively small numbers of patients who were not on statins at baseline and one[88] found a statistically significant effect of the intervention on medication initiation. However, in one study[86, 87] the intervention increased the number of patients who missed no doses in the last week. This same study also assessed medication persistence (the proportion of patients still on treatment at followup), but found no difference between the groups. However, this measure, while important to the goals of the study, was not a precise assessment of persistence. These results, although worthy of further investigation, provide no evidence of benefit for persistence and insufficient evidence for initiation or adherence (Table 11).

Other Outcomes

Both studies of decision aids evaluated patient satisfaction[86-88] and provide low strength of evidence that such decision aids improve aspects of patient satisfaction. One study found a two- to threefold increase in the intervention group's satisfaction with three aspects of their care: helpfulness of information, amount of information, and overall satisfaction.[86] Similarly, another study found statistically significantly less decisional conflict among intervention patients than control group patients.[88]

Detailed Synthesis for Health Coaching Interventions for Diabetes

Medication Adherence

One small study, conducted at one site assessed a program that included 14 telephone calls and a 6-month health coaching program, found no statistically significant effect on medication adherence at 12-month followup (Table 6).[89] Insufficient evidence exists to determine whether health coaching interventions can improve medication adherence among patients with diabetes (Table 12).

Detailed Synthesis for Social Support Interventions for Diabetes

Medication Adherence

One trial of this intervention among approximately 200 patients from 18 primary care practices in a statewide ambulatory practice-based research network showed no statistically significant difference between the social support intervention and educational controls regarding adherence (Table 6).[90] There is insufficientevidence that inclusion in diabetes education of a social support person selected by the diabetic patient improve medication adherence alone (Table 13).

Table 5. Medication adherence interventions for diabetes: study characteristics

Author, Year N at Randomization	Population Setting	Intervention and Comparator
Bogner et al., 2010[84] N=58	Adults over 50 years old with diabetes mellitus and depression Community-based primary care clinic	G1: Integrated care manager intervention G2: Usual care
Grantet al, 2003[85] N=462 N=232 in control and intervention arms excluding set aside lab controls	Adults with type 2 diabetes mellitus Academically-affiliated community health center	G1: Pharmacist-administered questionnaire assessing barriers to adherence and tailored verbal education, physician feedback, social service referrals G2: Pharmacist-administered questionnaire only G3: set aside lab controls.
Lin et al., 2006[83] N=329	Adults with diabetes mellitus and persistent depression Nine primary care clinics in Washington State	G1: Individualized management of depression G2: Standard of care of depression by primary care physician
Mann et al., 2010[88] N=150	Adult patients with diabetes mellitus Urban primary care practice	G1: *Statin Choice* decision aid G2: American Diabetes Association (ADA) print material
Pearce et al., 2005[90] N=199	Adults over 21 years old with type 2 diabetes mellitus and poorly controlled hypertension 18 primary care practices in the Kentucky Ambulatory Network practice-based research network	G1: One session of in-person nurse-delivered cardiovascular risk education with attendance of patient's social support person followed by mailing of quarterly educational newsletters G2: Same as G1 intervention G3: Same as G1 with exception of not involving patient's social support person for individual patient cardiovascular risk education session
Weymiller et al., 2007[86] Jones et al., 2009[87] N=98	Adults with type 2 diabetes mellitus Metabolic Specialty Clinic at Mayo Clinic	G1: *Statin Choice* decision aid G1a: Delivered by research staff before medical visit G1b: Delivered by clinician during medical visit G2: Standard of care educational pamphlet control G2a: Delivered by research staff before medical visit G2b: Delivered by clinician during medical visit
Wolever et al., 2010[89] N=56	Adults with type 2 diabetes mellitus on oral hypoglycemics Outpatient clinic at tertiary care center	G1: 6 months integrative health coaching G2: Usual care

Abbreviations: G, group; N, number.

Table 6. Medication adherence interventions for diabetes: medication adherence outcomes

Study N for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
Bogner et al., 2010[84] G1: 29 G2: 29	Number and percentage of participants achieving >80% adherence to medication at 6 weeks followup MEMS/Nonself-report	Oral hypoglycemics Baseline: n (%) G1: 10 (34.5) G2: 6 (20.7) 95% CI, NR p:0.19 Endpoint at 6 weeks: n (%) G1: 18 (62.1) G2: 7 (24.1) 95% CI, NR p:0.004 Antidepressant Baseline: n (%) G1: 8 (27.6) G2: 4 (13.8) 95% CI, NR p=0.17 Endpoint at 6 weeks: n (%) G1: 18 (62.1) G2: 3 (10.3) 95% CI, NR p<0.001
Grant et al., 2003[85] G1: 61 G2: 54	Difference from baseline to 3-month followup in number of days in the last 7 that no doses were missed (self-report)	G1: 0.1 (1) G2: 0.1 (0.4) 95% CI, NR p=0.8
Lin et al., 2006[83] G1: 164 G2: 165	Percentage of days nonadherent to medication at 12 months Pharmacy refill data (nonself-report)	Oral hypoglycemic agent Baseline Mean% (SD) G1: 19.8% (21.3%) G2: 22.9% (24.0%) 95% CI, NR p:NS Endpoint Mean% (SD) G1: 28.2% (28.9%) G2: 24.0% (24.7%) 95% CI, NR p<0.03 ACE inhibitor Baseline Mean% (SD) G1: 27.4% (27.1%) G2: 29.7% (29.3%) 95% CI, NR p:NS Endpoint Mean% (SD) G1: 24.2% (22.7%) G2: 18.9% (17.4%) 95% CI, NR p:NS Lipid-lowering agent Baseline Mean% (SD) G1: 29.3% (26.7%) G2: 24.5% (23.0%) 95% CI, NR p:NS

Table 6. Medication adherence interventions for diabetes: medication adherence outcomes (continued)

Study N for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
		Endpoint Mean% (SD) G1: 28.8% (27.1%) G2: 27.7% (24.0%) 95% CI, NR p:NS
	Adjusted mean difference in percentage of days nonadherent (baseline minus endpoint) Pharmacy refill data (nonself-report)	Oral hypoglycemic agent (%): -6.3 95% CI, -11.91 to -0.71 p:NS ACE inhibitor (%): -2.5 95% CI, -8.69 to 3.70 p:NS Lipid-lowering agent (%): -0.2 95% CI, -7.23 to 6.76 p:NS
Mann et al., 2010[88] G1: NR G2: NR	8-item Morisky Adherence Scale at 3 and 6 months to define percentage with “good adherence” (self-report)	3-month followup % with good adherence Full Group: 70% G1: NR G2: NR 95% CI, NR p:No significant difference between groups, 6-month followup Full Group: 80% G1: NR G2: NR 95% CI, NR p: No significant difference between groups,
	Started statins during visit (self-report)	G1: 9% G2: 0% 95% CI, NR p=0.01
	Started statins after visit (self-report)	G1: 3% G2: 4% 95% CI, NR p:NR
Pearce et al., 2005[90] G1: 50 G2: 58 G3: 91	4-item Morisky Adherence Scale at baseline and 12-month followup (self-report)	Baseline High (%): G1: 50.0 G2: 29.8 G3: 41.8 Medium (%): G1: 42.0 G2: 63.2 G3: 49.5 Low (%): G1: 8.0 G2: 7.0 G3: 8.8 95% CI, NR p (G1 vs. G2 vs. G3): 0.1584 p (G1 + G2 vs. G3): 0.4358

Table 6. Medication adherence interventions for diabetes: medication adherence outcomes (continued)

Study N for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
		Endpoint High (%): G1: NR G2: NR G3: NR Medium (%): G1: NR G2: NR G3: NR Low (%): G1: NR G2: NR G3: NR NS
Weymiller et al., 2007[86] Jones et al., 2009[87] *G1: 33 *G2: 29 *Number on statins at followup	Number of people who missed no doses in the last week 3 months after receiving the intervention (self-report)	G1: 31 G2: 23 OR: 3.4 95% CI, 1.5 to 7.5 p:NR
G1a:NR G1b:NR G2a:NR G2b:NR	Number of people who missed no doses in the last week 3 months after receiving the intervention by mode of delivery (self-report)	G1a: NR G1b: NR G2a: NR G2b: NR OR for mode of delivery: 0.8 95% CI, 0.3 to 2.6 p:NS
G1: 23 G2: 19	Statin therapy initiation among those not already receiving it (self-report)	Immediately after intervention (N (%)) G1: 7 (30) G2: 4 (21) 95% CI, NR; p:NR At 3-month followup (N (%)) G1: 9 (39) G2: 6 (32) 95% CI, NR; p:NR OR: 1.5 95% CI, 0.3 to 6.8 p:NR
G1: 52 G2: 46	Percentage using statins at followup (self-report)	N (%) G1: 33 (63) G2: 29 (63) 95% CI, NR p:NR OR: 1.4 95% CI, 0.8 to 2.4 p:NR

Table 6. Medication adherence interventions for diabetes: medication adherence outcomes (continued)

Study N for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
Wolever et al., 2010[89] G1: 27 G2: 22	4-item Morisky Adherence Scale at baseline and 6-month followup (self-report)	G1: Pre (Mean, SD): 6.7 (0.96) Post (Mean, SD): 7.2 (0.97) Within group change over time p=0.004 G2: Pre (Mean, SD): 6.7 (1.25) Post (Mean, SD): 6.9 (1.25) Within group change over time p=NS 95% CI, NR p-value for between group differences in change: NS
	One-item dichotomous question assessing whether patients missed dose in last 7 days (self-report)	G1: (% missing at least one dose) Pre: 51.9 Post: 7.4 Within group change over time: <0.001 G2: (% missing at least one dose) Pre: NR Post: NR Within group change over time: NS 95% CI, NR p:for between group differences NR

Abbreviations: ACE, angiotensin converting enzyme; CI, confidence interval; G, group; MEMS, Medication Event Monitoring System; N, number; NR, not reported, NS, not sufficient; OR, odds ratio; SD, standard deviation.

Table 7. Medication adherence interventions for diabetes: biomarker hemoglobin A1C (HbA1C)

Author, Year N in Each Group	Outcome	Results
Bogner et al., 2010[84] G1: 29 G2: 29	Biomarkers: HbA1c	Baseline (%) G1: Mean (SD): 7.3 (2.3) G2: Mean (SD): 7.3 (2.0) 95% CI, NR p=0.70 Endpoint (%) G1: Mean (SD): 6.7 (2.3) G2: Mean (SD): 7.9 (2.6) 95% CI, NR p=0.019

Abbreviations: CI, confidence interval; G, group; HbA1c, hemoglobin A1C; N, number; NR, not reported; SD, standard deviation.

Table 8. Medication adherence interventions for diabetes: other morbidity measures

Author, Year N in Each Group	Outcome	Results
Bogner et al., 2010[84] G1: 29 G2: 29	Depressive symptoms measured by 20-item CES-D higher scores indicate more severe depression	Baseline G1: Mean (SD): 15.6 (11.7) G2: Mean (SD): 19.7 (16.7) 95% CI, NR p=0.47 Endpoint G1: Mean (SD): 9.6 (9.4) G2: Mean (SD): 16.6 (14.5) 95% CI, NR p=0.035

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; G, group; N, number; NR, not reported; SD, standard deviation.

Table 9. Medication adherence interventions for diabetes: patient satisfaction

Author, Year N in Each Group	Outcome	Results
Mann et al., 2010[88] G1: NR G2: NR	Patient satisfaction: Decisional Conflict Scale--Informed subscale (range 0-100 with lower scores indicating less decisional conflict) Self-report	G1: 27.1 G2: 33.8 95% CI: NR P: 0.02
G1: NR G2: NR	Patient satisfaction: Decisional Conflict Scale--Support subscale (range 0-100 with lower scores indicating less decisional conflict) Self-report	G1: 25.2 G2: 29.6 95% CI: NR P: 0.05
G1: NR G2: NR	Patient satisfaction: Decisional Conflict Scale—Overall scale (range 0-100 with lower scores indicating less decisional conflict) Self-report	G1: 25.5 G2: 28.5 95% CI: NR P: 0.1
Weymiller et al., 2007[86] Jones et al., 2009[87] G1: 26 G2: 26 G3: 23 G4: 23	Patient satisfaction: Acceptable amount of information	N (%) responding 6 or 7 out of 7 G1: 23 (88) G2: 23 (92) G3: 16 (70) G4: 17 (74) 95% CI, NR; p:NR OR for decision aid (G1 & G2) vs. control (G3 & G4): 3.4 95% CI, 1.7 to 6.7; p:NR Mean (95% CI) G1: 7.0 (6 to 7) G2: 7.0 (6 to 7) G3: 7.0 (5 to 7) G4: 7.0 (5 to 7) 95% CI, NR; p:NR

Table 9. Medication adherence interventions for diabetes: patient satisfaction (continued)

Author, Year N in Each Group	Outcome	Results
	Patient satisfaction: Acceptable clarity of information	N (%) responding 6 or 7 of 7 G1: 19 (73) G2: 13 (52) G3: 12 (52) G4: 12 (52) 95% CI, NR p:NR OR for decision aid (G1 & G2) vs. control (G3 & G4): 1.6 95% CI, 0.8 to 3.2 p:NR Mean (95% CI) G1: 6.0 (5 to 7) G2: 6.5 (5 to 7) G3: 6.0 (4 to 7) G4: 6.0 (4 to 6) 95% CI, NR p:NR
	Patient satisfaction: Acceptable helpfulness of information	N (%) responding 6 or 7 of 7 G1: 18 (69) G2: 12 (48) G3: 8 (35) G4: 10 (43) 95% CI, NR p:NR OR for decision aid (G1 & G2) vs. control (G3 & G4): 2.3 95% CI, 1.4 to 3.8 p:NR Mean (95% CI) G1: 5.0 (4 to 7) G2: 7.0 (5 to 7) G3: 5.0 (4 to 7) G4: 5.0 (4 to 7) 95% CI, NR p:NR
	Patient satisfaction: Would recommend to others deciding on statins.	N (%) responding 6 or 7 of 7 G1: 21 (84) G2: 16 (64) G3: 13 (57) G4: 11 (50) 95% CI, NR p:NR OR for decision aid (G1 & G2) vs. control (G3 & G4): 2.6 95% CI, 0.8 to 8.0 p:NR Mean (95% CI) G1: 6.0 (4 to 7) G2: 7.0 (7 to 7) G3: 5.5 (4 to 7) G4: 6.0 (5 to 7) 95% CI, NR p:NR

Table 9. Medication adherence interventions for diabetes: patient satisfaction (continued)

Author, Year N in Each Group	Outcome	Results
	Patient satisfaction: Would prefer similar approach for other treatment choices	N (%) responding 6 or 7 of 7 G1: 18 (72) G2: 16 (64) G3: 14 (61) G4: 12 (55) 95% CI, NR p:NR OR for decision aid (G1 & G2) vs. control (G3 & G4): 1.5 95% CI, 0.6 to 3.8 p:NR Mean (95% CI) G1: 6.0 (4 to 7) G2: 7.0 (5 to 7) G3: 6.0 (4 to 7) G4: 6.0 (4 to 7) 95% CI, NR p:NR
	Patient satisfaction: Overall acceptability	N (%) responding 6 or 7 of 7 G1: 20 (77%) G2: 14 (56%) G3: 9 (39%) G4: 10 (43%) 95% CI, NR p:NR OR for decision aid (G1 & G2) vs. control (G3 & G4): 2.8 95% CI, 1.2 to 6.9 p:NR Mean (95% CI) G1: 6.0 (4.6 to 6.6) G2: 6.6 (6.0 to 7.0) G3: 5.4 (4.6 to 6.8) G4: 5.4 (4.6 to 6.6) 95% CI, NR p:NR

Abbreviations: CI, confidence interval; G, group; N, number; NR, not reported; OR, odds ratio.

Table 10. Care coordination or collaborative care for diabetes: strength of evidence

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Study Design/ Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Coordinated care vs. usual care	3; 507 (507)	Medication Adherence	RCT Medium	Consistent	Direct	Precise	Varied measures and magnitude Low
	1; 58 (58)	Biomarker: HbA1c	RCT Low	Not applicable	Direct	Precise	Difference between groups 1.2 Low
	1; 58 (58)	Morbidity: Depressive Symptoms (CES-D)	RCT Low	Not applicable	Direct	Precise	Difference between groups 7.0 Low

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; HbA1C, hemoglobin A1C; RCT, randomized controlled trial.

Table 11. Decision aids for diabetes: strength of evidence

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Study Design/ Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Statin decision aid vs. standard written information about lipids	2; 248 (NR)	Medication adherence	RCT Medium	Inconsistent	Direct	Imprecise	Insufficient
	2,248 (NR)	Medication Initiation	RCT Medium	Inconsistent	Direct	Imprecise	Insufficient
	2;248 (NR)	Patient satisfaction	RCT Medium	Consistent	Direct	Imprecise	Low

Abbreviations: NR, not reported; RCT, randomized controlled trial.

Table 12. Health coaching for diabetes: strength of evidence

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Study Design/ Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Health coaching vs. usual care	1; 56 (49)	Adherence	RCT Medium	NA	Direct	Precise	Difference between groups on 4-point scale: 0.3 Insufficient

Abbreviations: NA, not applicable; RCT, randomized controlled trial.

Table 13. Social support for diabetes: strength of evidence

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Study Design/ Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Social Support with patient education vs. patient education without social support	1; 199 (189)	Adherence	RCT Medium	NA	Direct	Precise	Endpoint value NR Low

Abbreviations: NA, not applicable; NR, not reported; RCT, randomized controlled trial.

Key Question 1. Hyperlipidemia: Medication Adherence Interventions

Description of Included Studies

Overview

We found ten articles comprising nine studies that evaluated interventions to improve medication adherence among patients with hyperlipidemia.[74, 83, 86-88, 91-95] We rated all nine studies as having medium risk of bias. Table 14 presents an overview of the interventions. Table 15 through Table 17 present results for medication adherence and other outcomes for all studies, followed by strength of evidence tables by type of intervention (Table 18, Table 19, and Table 11).

Population

Three of the studies were conducted primarily among patients with elevated cholesterol,[92-94] one was among patients both with elevated risk of a first myocardial infarction and elevated cholesterol,[91] two were among patients with diabetes,[86-88] and three studies evaluated subgroups with hyperlipidemia.[74, 83, 95] All studies were conducted in adults with inclusion ages ranging from 21 years or older[93, 94] to 65 years or older.[74] In the seven studies that reported mean participant ages,[74, 83, 86-88, 91, 92, 95] the range was from 54–55 years old[95] to 78 years old.[74] In the studies reporting proportion of female participants,[74, 83, 86-88, 91, 93-95] women comprised between 22.9 percent[74] and 65–68 percent[95] of the study populations. The most commonly reported

categories of race and ethnicity were Caucasian and African-American. African-American participants comprised between 5.8 percent[94] and 32.3 percent[74] of the study populations in the three studies that reported this information.[74, 91, 94]

Intervention

The nine studies evaluated diverse interventions that were all targeted at patients. One study additionally targeted systems of care.[92] Interventions in three studies[91-93] included a component of telephone calls that served different purposes. In one study the telephone calls served primarily as reminders;[91] in another study the calls were to address problems and adverse events associated with medications;[92] and in the third study, the calls delivered tailored behavioral support interventions via an interactive voice recognition (IVR) system.[93] Two interventions that included telephone calls also mailed printed materials either to reinforce general recommendations[91] or to specifically reinforce medication adherence.[93] One of the telephone-based studies additionally provided a free 2-week supply of medication and recommendations for participants from physicians.[91] Among the remaining studies, interventions in two studies were primarily delivered by mail. One of the mail-based interventions consisted of an individualized, stage-matched expert system intervention and manual for adherence to lipid-lowering medication based on the transtheoretical model for change.[94] The other mail-based intervention delivered one of four educational videotape programs to participants by mail that provided educational information on the patients' inferred disease/condition process, medication(s), and the importance of adherence.[95] Two studies tested a decision aid aimed at cardiovascular risk reduction choices.[86-88] One study evaluated the effect of collaborative care, leading to individualized management for depression with either antidepressant medication or problem-solving treatment on adherence to multiple classes of medications, including angiotensin-converting enzyme (ACE) inhibitors in a subgroup with hypertension.[83] The final intervention was a continuation of a multicomponent pharmacy-based intervention including clinical pharmacist delivery of individualized medication education and blister packing of medications.[74]

Comparator

Active arms were compared with usual care in four of the nine studies.[83, 92, 94, 95] In two of these studies, usual care consisted of not receiving mailed intervention materials;[94, 95] in one study, usual care consisted of advising participants to consult their primary care physician for treatment,[83] and in the fourth study, usual care consisted of receiving no phone calls following an initial clinic visit.[92] In one of the remaining five studies, the control group received a free 2-week supply of medication and recommendations from physicians (also received by the intervention group) and two reminder postcards to reinforce recommendations (compared with four postcards in the intervention group) but no telephone calls (two calls were delivered to the intervention group).[91] In another study, after a 6-month phase in which both intervention and control groups received an intervention that included blister packing of medications and pharmacist visits, the intervention was discontinued for the control group, which then received medications in pill bottles with a 90-day supply.[74] In another study, the control group received nontailored behavioral advice from a single interactive voice recognition call at baseline, coupled with a nontailored, generic, self-help cholesterol management guide received through the mail that did not address medication persistence or adherence.[93] In the final two studies evaluating statin decision aids, usual care patients received control educational printed materials.[86-88]

Outcome and Timing

Only one of the nine studies reported on initiation of medication.[86, 87] Three studies reported on persistence of medication use; two studies used persistence measures from pharmacy refill or claims data[92, 93] and the other used self-reported persistence measures at 3 months following the intervention.[86, 87] Of the studies using pharmacy refill data to report persistence, one study reported persistence in two ways: (1) being in possession of a statin prescription at the end of a 180-day observation period and (2) having no gaps of more than 30 days in statin refills over 6 months;[93] the other study reported persistence as the proportion of participants refilling prescriptions for either niacin or a bile acid sequestrant (BAS) at 2 months.[92] All nine studies reported medication adherence outcomes. Measures of adherence included pharmacy refill data in three studies,[83, 93, 95] pill counts in one study,[74] and self-reported measures in five studies.[86-88, 91, 92, 94] One study used multiple measures: pharmacy refill data to report persistence and a self-reported measure to report adherence.[92] Three of four studies with nonself-reported adherence measures described proportions with 80 percent or greater adherence as determined by medication possession ratios (MPR) from pharmacy refill data in two studies[93, 95] and by pill count in one study.[74] Self-reported adherence measures were ascertained through adherence-related questions in three studies[86, 87, 91, 92] and a Morisky scale in one study.[88] In addition, one study ascertained self-reported adherence measures from both a stage of change algorithm and medication adherence scale scores.[94]

Of the four studies with either improved medication adherence or persistence outcomes,[74, 86, 87, 93, 94] three reported additional outcomes that included LDL-C levels and changes in LDL-C levels from baseline to followup in one study[74] and patient satisfaction in two other studies.[86-88]

The duration of interventions varied among the four studies; the shortest intervention lasted 3 months[86, 87] and the longest lasted 18 months.[94] One study reported adherence and persistence outcomes from 2 months, although the intervention was 6 months.[92] Two studies reported adherence at points during and at the conclusion of the intervention.[88, 94] One study reported adherence measured 3 months following the conclusion of the intervention.[86, 87] The other five studies reported adherence as it was measured at the conclusion of the intervention,[91] or reported average adherence or persistence measured throughout the intervention.[74, 83, 93, 95] In the study that reported LDL-C measures, outcomes were measured at the conclusion of the intervention (14 months); changes in LDL-C levels from 2–14 months were also reported. Of note, this study lasted a total of 14 months with an initial 2-month run-in period followed by a 6-month cohort intervention in which both groups received the intervention followed by a final 6-month randomized controlled trial in which one group continued the prior intervention and one group discontinued the intervention.[74] Two studies that reported patient satisfaction measures obtained outcomes immediately following the intervention.[86-88]

Setting

Settings varied among the nine studies. Three studies were based in primary care clinics,[83, 88, 91] one of which was within a pharmaceutical registry.[91] One study was based out of a metabolic specialty clinic.[86, 87] Two studies were based in either a military medical center[74] or a Veterans Administration medical center.[92] Two studies were conducted among either HMO or PPO members.[93, 95] The final study recruited participants from multiple sources: random-digit dialing, a pre-existing database of potential participants from prior studies, a large Massachusetts health plan, and health screenings or health fairs.[94]

Applicability

Notable limitations to applicability included studies that were conducted only among select populations such as participants in a registry program who received a free 2-week supply of pravastatin,[91] HMO or PPO members in two studies,[93, 95] patients cared for at a military medical center in one study[74] and patients cared for at a Veterans Administration medical center in one study.[92] After randomization, one study additionally eliminated participants who had no intention of picking up a statin prescription, were not aware of the prescription, or failed to answer at least 50 percent of the baseline assessment, which may have introduced selection bias.[93]

Key Points

Overview

- Medication adherence: Across nine studies, we found mixed evidence for medication adherence or persistence. Four of nine studies found improvements in outcomes of either medication adherence or persistence.
- Medication initiation: Only one study with a small sample size found an improvement in medication initiation.
- Other outcomes: Two of the four studies with either improved medication adherence or persistence outcomes reported additional outcomes; one reported LDL-C and the other reported patient satisfaction.

Telephone-based Interventions

- Medication adherence: We found limited evidence for improved medication adherence or persistence among the three studies with a component of telephone calls with heterogeneous, imprecise outcomes (low strength of evidence).
- For all other outcomes, we judged the evidence to be insufficient due to lack of evidence (insufficient evidence).

Mail-based Educational Interventions

- Medication adherence: We found mixed evidence for improved medication adherence among the two studies delivered by mail. The two studies used variable measures to assess medication adherence: some were indirect (stage of change algorithm) and others had imprecise outcomes (low strength of evidence).
- For all other outcomes, we judged the evidence to be insufficient due to lack of evidence (insufficient evidence).

Collaborative Depression Care

- Medication adherence: The one study that evaluated collaborative depression care had imprecise adherence outcomes with small sample sizes (insufficient evidence).

Statin Decision Aids

- Medication initiation: The two studies of decision aids found mixed evidence of improved medication initiation among intervention group with imprecise outcomes and small sample sizes (insufficient evidence).
- Medication adherence: The two studies also found imprecise outcomes for improved medication adherence with small sample sizes (insufficient evidence).

- Decision aid interventions improve patient satisfaction with some aspect of their care (low strength of evidence).For all other outcomes, we judged the evidence to be insufficient due to lack of evidence (insufficient evidence).

Pharmacist-led Multicomponent Intervention

- Medication adherence: One small study reported improved medication adherence, but had different timing of measurement of the adherence outcome between groups (insufficient evidence).
- Biomarkers: No difference was noted between groups in LDL-C outcomes (insufficient evidence).

Detailed Synthesis for Hyperlipidemia for Interventions with a Telephone-based Component

Medication Adherence

Among the three interventions that included a component of telephone calls,[91-93] one identified improved adherence as measured by 80 percent or more medication possession ratio over 6 months in the intervention group (47.0 percent) compared with the control group (38.9 percent, adjusted odds ratio 1.43; Table 15); however, this study used a cutoff of $p<0.10$ for statistical significance. Among the same three telephone interventions, two reported medication persistence outcomes,[92, 93] and only one found improvements in persistence as measured by the proportion in possession of a statin at the end of the 180-day intervention in the intervention group (70.4 percent) compared with the control group (60.7 percent, adjusted odds ratio 1.64, $p<0.05$).[93] Other measures of persistence that were improved in the intervention group compared with the control group in this study included the proportion of each group without a gap of more than 30 days in statin prescription refills (G1: 52.2 percent, G2: 44.3 percent, $p<0.10$) and the proportion both without a gap of more than 30 days in statin prescription refills and medication possession ratio of 80 percent or more over months (G1: 45.1 percent, G2: 37.3 percent, $p<0.10$).[93] Given that only one of the three studies found improved persistence or adherence, the variability of measures, and imprecision in outcomes, evidence of improved adherence was graded as low (Table 18).

Other Outcomes

We did not evaluate other health outcomes for this intervention type because the one study that demonstrated improved adherence and persistence did not evaluate additional outcomes.

Detailed Synthesis for Hyperlipidemia for Interventions with a Mail-based Educational Component

Medication Adherence

Among the two mail-based studies,[94, 95] one identified improved adherence in the intervention group compared with the control group (Table 15).[94] This study evaluated adherence among participants who received a mail-based intervention as reaching or maintaining an "Action" stage (having improved adherence for less than 6 months) or "Maintenance" stage (having improved adherence for more than 6 months) by self-report in a stage of change algorithm.[94] Among a "pre-action" portion of the study sample, the proportion reaching Action

or Maintenance was higher at 6 and 18 months, but not at 12 months, in the intervention group compared with the control group. Among a "post-action" sample, the proportion maintaining Action or Maintenance was higher only at 18 months in the intervention group compared with the control group. Other statistically significant differences between intervention and control groups were identified among the pre-action portion of the sample in (1) a self-reported 4-item Medication Adherence Scale scores at 6, 12, and 18 months and (2) in a 5-item mean level of adherence score at 12 and 18 months.[94] The mail-based study of educational videotapes that did not find improved adherence in MPR or proportion with MPR of 80 percent or more between intervention and control groups.[95] Because the two studies used variable measures to assess medication adherence, some of which were indirect (stage of change algorithm), and imprecise outcomes, we graded the strength of evidence of benefit from this body of evidence as low (Table 19).

Other Outcomes

We did not evaluate other health outcomes for this intervention type because the one study that demonstrated improved adherence measures did not evaluate additional outcomes.

Detailed Synthesis for Hyperlipidemia for Collaborative Care

Medication Adherence

The study of a collaborative care model resulting in individualized management of depression care found slightly worsened adherence to oral hypoglycemic medications in the intervention group compared with the control group over 12 months, but did not identify a difference between groups for ACE inhibitor or lipid-lowering agent adherence in subgroup analyses (Table 15).[83] Because this study had imprecise adherence outcomes with small sample sizes, we felt the evidence was insufficient to grade.

Detailed Synthesis for Hyperlipidemia for Statin Decision Aids

Medication Adherence

Of the two studies of statin decision-aid interventions,[86-88] one found improved self-reported medication persistence in the intervention group compared with the control group, but only among the subgroup on statins at 3 months following the intervention (

Table 15).[86, 87] While the other study of statin decision aids did not find improved adherence in the intervention group, improved statin initiation was found in the intervention group (9 percent) compared with the control group (0 percent).[5] In this study, medication initiation was measured by a survey following a baseline clinic visit during which the statin decision aid was administered to the intervention group. Because of small sample sizes and imprecise outcomes in medication initiation, adherence, and persistence, we could not judge the true effect of the intervention and rated the evidence as insufficient (Table 11).

Other Outcomes

Both studies reported patient satisfaction outcomes.[86-88] One study found improved outcomes in the intervention arm compared with the control arm for subscales of the Decisional Conflict Scale, including the informed and support subscales.[88] The other study found that the intervention group reported significantly higher satisfaction than control groups for the following

self-reported items pertaining to the decision aid: acceptable amount of information, acceptable helpfulness of information, and overall acceptability (Table 17).[86, 87] Because the evidence came from a small sample and satisfaction outcomes were imprecise, the body of evidence was graded as low.

Detailed Synthesis for Hyperlipidemia for Pharmacist-led Multicomponent Intervention

Medication Adherence

The one pharmacist intervention found improved medication adherence outcomes in the intervention group compared with the control group.[74] This study evaluated adherence from pill counts both as the percent medication adherence in the intervention arm (95.5 percent) versus the control arm (69.1 percent) at 6 months and as the proportion of participants with 80 percent or greater adherence in the intervention arm (97.4 percent) compared with the control arm (21.7 percent) over 6 months (Table 15).[74] However, pill counts were performed less frequently in the control arm (once over 6 months) than the intervention arm (three times over 6 months). Since adherence outcomes were at risk of bias in this relatively small, single study, we deemed the evidence for pharmacist interventions insufficient to grade.

Other Outcomes

This study also reported LDL-C outcomes and found no statistically significant differences either in LDL-C between intervention (87.5) and control groups (88.4) at 14 months or in changes in LDL-C from 2 months to 14 months between intervention (-2.8) or control groups (-5.8) (Table 16). The conclusion of insufficient evidence of effectiveness of this intervention for improvements of LDL-C needs to be evaluated in the context of the relatively small, single trial that found improved medication adherence and evaluated these outcomes.

Table 14. Hyperlipidemia: study characteristics

Author, Year N at randomization	Population Setting	Intervention and Comparator
Guthrie et al., 2001[91] N=13,100	Adults with elevated risk of a first myocardial infarction and elevated cholesterol Primary care clinics	G1: Received a free 2-week supply of Pravastatin, lifestyle and medication recommendations from physicians, two telephone reminders, and four reminder postcards to reinforce coronary risk reduction recommendations G2: Received a free 2-week supply of Pravastatin, lifestyle and medication recommendations from physicians, no telephone calls, and two reminder postcards to reinforce coronary risk reduction recommendations
Johnson et al., 2006[94] N=404	Adults ages 21–85 prescribed cholesterol medication Mail-based intervention	G1: A computer-generated, individualized, stage-matched expert system intervention and manual for adherence to lipid-lowering medication based on the transtheoretical model for change. Printed feedback was provided at followup G2: Did not receive intervention materials
Lee et al., 2006[74] N=159	Adults ≥65 years old taking four or more daily medications, most with hypertension and hyperlipidemia Pharmacy within a U.S. military medical center	G1: Continuation of multicomponent pharmacy-based intervention including clinical pharmacist delivery of individualized medication education every 2 months and blister packing of medications G2: Discontinuation of intervention, medications provided in pill bottles with a 90-day supply
Lin et al., 2006[83] N=329	Adults with diabetes mellitus and persistent depression Primary care clinics	G1: Collaborative care with individualized management of depression care using one of two evidence-based treatments: antidepressant medication or problem-solving treatment G2: Advised to consult primary care physician for depression treatment
Mann et al., 2010[88] N=150	Adult patients with diabetes mellitus Urban primary care practice	G1: Statin choice decision aid G2: ADA print material
Powell et al., 1995[95] N=4246	Members of a large Midwestern HMO; had a pharmacy claim for benazepril, metoprolol, simvastatin, or transdermal estrogen Homes	G1: Subjects mailed one of four educational videotape programs presenting information on the patients' inferred disease/condition process, suggesting behavior changes, how their prescribed drug works, and why adherence is important G2: Received no educational materials
Schectman et al., 1994[92] N=102 (Niacin) N=62 (Bile acid sequestrant)	Adults with hyperlipidemia requiring treatment with either niacin or a bile acid sequestrant VA medical center	G1: Following initial clinic visit, received five calls over 28 days from a certified medical assistant to address problems and adverse events associated with medications, when needed; additional telephone contact arranged with physician or clinical pharmacist G2: No telephone contact following initial clinic visit
Stacy et al., 2009[93] N=578	Adults ≥21 years old with a new statin prescription HMO or PPO members	G1: Received up to three separate tailored behavioral support interventions delivered via an IVR system coupled with tailored print material received through the mail that specifically reinforced adherence/persistence with statins G2: Received nontailored behavioral advice from a single IVR call at baseline, coupled with a nontailored, generic, self-help cholesterol management guide received through the mail that did not address medication persistence/adherence.

Table 14. Hyperlipidemia: study characteristics (continued)

Author, Year N at randomization	Population Setting	Intervention and Comparator
Weymiller et al., 2007[86] Jones et al., 2009[87] N=98	Adults with Type 2 diabetes mellitus Metabolic specialty clinic at Mayo Clinic	G1: Statin choice decision aid G1a: delivered by research staff before medical visit G1b: delivered by clinician during medical visit G2: Standard of Care Educational Pamphlet Control G2a: delivered by research staff before medical visit G2b: delivered by clinician during medical visit

Abbreviations: ADA, American Diabetes Association; G, group; HMO, health maintenance organization; IVR, interactive voice recognition; N, number; PPO, preferred provider organization; US, United States; VA, Veterans Administration.

Table 15. Hyperlipidemia: medication adherence

Study N analyzed for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
Guthrie et al., 2001[91] G1: 3635 G2: 913	Medication compliance survey: currently taking pravastatin as prescribed (proportion answering yes) Self-report	G1: 79.7% G2: 77.4% 95% CI, NR p: NR
G1: 3635 G2: 913	Medication compliance survey (proportion indicating that no doses missed in the past 7 days) Self-report	G1: 64.3% G2: 61.8% 95% CI, NR p: NR
Johnson et al., 2006[94] G1: Not reported G2: Not reported	In pre-action portion of sample: Proportion reaching Action or Maintenance stage for medication adherence with eight-item stage of change algorithm Results ranged with regard to medication adherence change as follows: Pre-contemplative (not intending to become adherent), Contemplative (intending to become adherent in the next 6 months), Preparation (intending to become adherent in the next 30 days), Action (having improved adherence for <6 months), and Maintenance (having improved adherence for >6 months) Self-report	Baseline: no significant difference, no numbers reported, in figure only; p>0.05 6 months: G1: 55.3% G2: 40.0% OR (G1 to G2): 1.80 95% CI, NR p<0.05 12 months: no percentages reported, in figure only; p=0.057 18 months: G1: 56.0% G2: 37.8% OR: NR 95% CI, NR p<0.01

Table 15. Hyperlipidemia: medication adherence (continued)

Study N analyzed for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
G1: Not reported G2: Not reported	In pre-action portion of sample: Medication Adherence Scale Score on 4-item scale (higher scores represent better adherence) Self-report	Baseline: no significant difference, no numbers reported, in figure only; 95% CI, NR p >0.05 6 months: no numbers reported, in figure only OR (G1 to G2): 1.49 95% CI, NR p<0.01 12 months: no numbers reported, in figure only OR (comparing G1 to G2): 1.62 95% CI, NR p<0.001 18 months: no numbers reported, in figure only OR (comparing G1 to G2): 1.62 95% CI, NR p<0.01
G1: Not reported G2: Not reported	In pre-action portion of sample: Mean level of adherence score on 5-item survey measuring nonadherence (lower scores represent better adherence) Self-report	Baseline: no significant difference, no numbers reported, in figure only; 95% CI, NR p not reported 6 months: no numbers reported, in figure only OR (comparing G1 to G2): 2.03 95% CI, NR p>0.05 12 months: no numbers reported, in figure only OR (comparing G1 to G2): 3.67 95% CI, NR p<0.01 18 months: no numbers reported, in figure only OR (comparing G1 to G2): 2.86 95% CI, NR p<0.05

Table 15. Hyperlipidemia: medication adherence (continued)

Study N analyzed for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
G1: Not reported G2: Not reported	In post-action portion of sample: Proportion Maintaining Action or Maintenance stage for adherence on 5-item survey with stage of change algorithm (Action defined as having improved adherence for < 6 months; Maintenance defined as having improved adherence for > 6 months) Self-report	Baseline: no significant difference, no numbers reported, in figure only; 95% CI, NR p: NR 6 months: no numbers reported, in figure only OR (G1 to G2): 2.12 95% CI, NR p>0.05 12 months: no numbers reported, in figure only, OR NR 95% CI, NR p>0.05 18 months: G1: 85.0% G2: 55.6% OR: NR 95% CI, NR p<0.01
Lee et al., 2006[74] G1: 83 G2: 76	Percentage medication adherence for 6 months (proportion of pills taken), mean (SD) Pill count	G1: 95.5 (7.7) G2: 69.1 (16.4) 95% CI, NR p<0.001
G1: 83 G2: 76	Percentage with ≥ 80% adherence to all medications over 6 months Pill count	G1: 97.4 G2: 21.7 95% CI, NR p<0.001
Lin et al., 2006[83] G1: 164 G2: 165	Percentage of days nonadherent to medication at 12 months Pharmacy refill data	Oral hypoglycemic agent Baseline (%) (Mean (SD)) G1: 19.8% (21.3%) G2: 22.9% (24.0%) 95% CI, NR p: NS Endpoint (%) (Mean (SD)) G1: 28.2% (28.9%) G2: 24.0% (24.7%) 95% CI, NR p:<0.03 ACE inhibitor Baseline (%) (Mean (SD)) G1: 27.4% (27.1%) G2: 29.7% (29.3%) 95% CI, NR p: NS Endpoint (%) (Mean (SD)) G1: 24.2% (22.7%) G2: 18.9% (17.4%) 95% CI, NR p: NS

Table 15. Hyperlipidemia: medication adherence (continued)

Study N analyzed for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
		Lipid-lowering agent Baseline (%) (Mean (SD)) G1: 29.3% (26.7%) G2: 24.5% (23.0%) 95% CI, NR p: NS Endpoint (%) (Mean (SD)) G1: 28.8% (27.1%) G2: 27.7% (24.0%) 95% CI, NR p: NS
	Adjusted mean difference in percentage of days nonadherent (baseline minus endpoint) Pharmacy refill data	Oral hypoglycemic agent (%)=-6.3% 95% CI, -11.91 to -0.71 p: <0.03 ACE inhibitor (%)=-2.5% 95% CI, -8.69 to 3.70 p: NS Lipid-lowering agent (%)=-0.2 95% CI, -7.23 to 6.76 p: NS
Mann, et al., 2010[88] G1: NR G2: NR	8-item Morisky Adherence Scale at 3 and 6 months to define percentage with "good adherence" Self-report	3 months followup Full group: 70% G1: NR G2: NR 95% CI, NR p: No significant difference between groups 6 months followup Full group: 80% G1: NR G2: NR 95% CI, NR p: No significant difference between groups,
	Prescribed statin during visit (proportion answering yes following baseline visit) Self-report	Baseline: G1: 9% G2: 0% 95% CI, NR p=0.01
	Prescribed statin after visit (proportion answering yes following baseline visit) Self-report	Baseline: G1: 3% G2: 4% 95% CI, NR p: NR

Table 15. Hyperlipidemia: medication adherence (continued)

Study N analyzed for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
Powell et al., 1995[95] N=4246 G1: 1993 G2: 2253	MPR Pharmacy refill data	Over a 9-month period: Overall (Mean (SD)) G1: 0.70 (0.23) G2: 0.70 (0.28) 95% CI, NR p: NR
G1: 175 G2: 243		Benazepril (Mean (SD)) G1: 0.71 (0.25) G2: 0.72 (0.26) 95% CI, NR p: NR
G1: 717 G2: 823		Transdermal estrogen (Mean (SD)) G1: 0.60 (0.32) G2: 0.58 (0.32) 95% CI, NR p: NR
G1: 830 G2: 898		Metoprolol (Mean (SD)) G1: 0.74 (0.27) G2: 0.73 (0.28) 95% CI, NR p: NR
G1: 271 G2: 297		Simvastatin (Mean (SD)) G1: 0.73 (0.26) G2: 0.70 (0.28) 95% CI, NR p: NR
G1: 1993 G2: 2253	Compliance (MPR $\geq$0.80) Pharmacy refill data	Over a 9-month period: Overall (N (%)) G1: 917 (46%) G2: 998 (44%) 95% CI, NR p: NR
G1: 175 G2: 243		Benazepril (N (%)) G1: 78 (45%) G2: 104 (44%) 95% CI, NR p: NR
G1: 717 G2: 823		Transdermal estrogen (N (%)) G1: 266 (37%) G2: 209 (35%) 95% CI, NR p: NR

Table 15. Hyperlipidemia: medication adherence (continued)

Study N analyzed for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
G1: 830 G2: 898 G1: 271 G2: 297		Metoprolol (N (%)) G1: 438 (53%) G2: 466 (52%) 95% CI, NR p: NR Simvastatin (N (%)) G1: 135 (50%) G2: 138 (46%) 95% CI, NR p: NR
Schectman et al., 1994[92] Niacin: G1: 40 G2: 40 BAS: G1: 18 G2: 22	Answer to question: "During the past week, how many doses of your medication have you missed?" (Proportion measured not described) Self-report	At 2 months: Niacin: G1: 76 (SD 5) G2: 77 (SD 6) 95% CI, NR p: 0.85 BAS: G1: 76 (SD 7) G2: 60 (SD 9) 95% CI, NR p: 0.14
Niacin: G1: 40 G2: 40 BAS: G1: 18 G2: 22	Proportion refilling prescription at 2 months Pharmacy refill data	Niacin (Mean (SD)): G1: 90% (2) G2: 84% (3) 95% CI, NR p: 0.07 BAS (Mean (SD)): G1: 88% (4) G2: 82% (4) 95% CI, NR p: 0.32
Stacy et al., 2009[93] G1: 253 G2: 244	MPR ≥80% over 6 months (filled: prescribed) Pharmacy refill data	G1: 47.0% G2: 38.9% Unadjusted OR, 1.39 90% CI, 1.03-1.88 Adjusted OR, 1.43 90% CI, 1.05-1.96 p: <0.10
G1: 253 G2: 244	Persistence: subject being in possession of a statin at the end of the 180-day observation period Pharmacy refill data	G1: 70.4% G2: 60.7% Unadjusted OR, 1.54 90% CI, 1.13-2.10 Adjusted OR, 1.64 90%CI, 1.19-2.26 p: <0.05
G1: 253 G2: 244	Continuous Persistence: having any statin prescription dispensed at least every 30 days after the end date of a previous prescription for a statin (no gaps >30 days) at 6 months Pharmacy refill data	G1: 52.2% G2: 44.3% Unadjusted OR, 1.37 90% CI, 1.02-1.85 Adjusted OR, 1.41 90%CI, 1.05-1.94 p: <0.10

Table 15. Hyperlipidemia: medication adherence (continued)

Study N analyzed for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
G1: 253 G2: 244	Both Continuous Persistence (as defined above) and Medication Possession Ratio ≥80% over 6 months (filled: prescribed) Pharmacy refill data	G1: 45.1% G2: 37.3% Unadjusted OR, 1.38 90% CI, 1.03-1.86 Adjusted OR, 1.41 90% CI, 1.03-1.92 p: <0.10
Weymiller, et al., 2007[86] Jones, et al., 2009[87] *G1: 33 *G2: 29 *number on statins at followup	Number of people who missed no doses in the last week 3 months after receiving the intervention Self-report	G1: 31 G2: 23 Odds ratio: 3.4 95% CI, 1.5-7.5 p: NR
G1a:NR G1b:NR G2a:NR G2b:NR	Number of people who missed no doses in the last week 3 months after receiving the intervention by mode of delivery Self-report	G1a:NR G1b:NR G2a:NR G2b:NR Odds ratio for mode of delivery: 0.8 95% CI, 0.3, 2.6 p:NS
G1: 23 G2: 19	Statin therapy initiation among those not already receiving it Self-report	Immediately after intervention (N (%)) G1: 7 (30%) G2: 4 (21%) 95% CI, NR; p: NR At 3-month followup (N (%)) G1: 9 (39%) G2: 6 (32%) 95% CI, NR; p: NR Odds ratio: 1.5 95% CI, 0.3 to 6.8; p: NR
G1: 52 G2: 46	Percentage using statins at followup Self-report	N (%) G1: 33 (63%) G2: 29 (63%) 95% CI, NR p: NR Odds ratio: 1.4 95% CI, 0.8 to 2.4 p: NR

Abbreviations: CI, confidence interval; G, group; MPR, medication possession ratio; NR, not reported; NS, not significant; OR, odds ratio; SD, standard deviation.

Table 16. Hyperlipidemia: biomarkers

Author, Year N in Each Group	Outcome	Results
Lee et al., 2006[74]		
G1: 64 G2: 57	Among patients with drug-treated hyperlipidemia: LDL-C at 14 months	G1: 87.5 mean (SD 24.2) G2: 88.4 mean (SD 21.0) p=0.84
G1: 64 G2: 57	Among patients with drug-treated hyperlipidemia: difference between LDL-C at 2 months and 14 months	G1: -2.8 (95% CI, -8.1 to 2.5) G2: -5.8 (95% CI, -11.0 to 0.6) p=0.85
G1: 73 G2: 62	Among patients with drug-treated hypertension: systolic blood pressure at 14 months	G1: 124.4 mm Hg (SD 14.0) G2: 133.3 mm Hg (SD 21.5) p=0.005
G1: 73 G2: 62	Among patients with drug-treated hypertension: difference between systolic blood pressure measures at 2 months and 14 months	G1: -6.9 mm Hg (95% CI, -10.7 to -3.1) G2: -1.0 mm Hg (95% CI, -5.9 to 3.9) p=0.04
G1: 73 G2: 62	Among patients with drug-treated hypertension: diastolic blood pressure at 14 months	G1: 67.5 mm Hg (SD 9.9) G2: 68.6 mm Hg (SD 10.5) p=0.54
G1: 73 G2: 62	Among patients with drug-treated hypertension: difference between diastolic blood pressure measures at 2 months and 14 months	G1: -2.5 mm Hg (SD -4.9 to -0.2) G2: -1.2 mm Hg (SD -3.7 to 1.2) p=0.39

Abbreviations: G, group; LDL-C, Low-density lipoprotein cholesterol; SD, standard deviation.

Table 17. Hyperlipidemia: patient satisfaction

Author, Year N in Each Group	Outcome	Results
Mann et al., 2010[88] G1: NR G2: NR	Patient satisfaction: Decisional Conflict Scale--Informed subscale (range 0-100 with lower scores indicating less decisional conflict) Self-report	G1: 27.1 G2: 33.8 95% CI: NR P: 0.02
G1: NR G2: NR	Patient satisfaction: Decisional Conflict Scale--Support subscale (range 0-100 with lower scores indicating less decisional conflict) Self-report	G1: 25.2 G2: 29.6 95% CI: NR P: 0.05
G1: NR G2: NR	Patient satisfaction: Decisional Conflict Scale—Overall scale (range 0-100 with lower scores indicating less decisional conflict) Self-report	G1: 25.5 G2: 28.5 95% CI: NR P: 0.1

Table 17. Hyperlipidemia: patient satisfaction (continued)

Author, Year N in Each Group	Outcome	Results
Weymiller et al., 2007[86] Jones et al., 2009[87] G1: 26 G2: 26 G3: 23 G4: 23	Patient satisfaction: Acceptable amount of information (higher scores indicate better satisfaction) Self-report	N (%) responding 6 or 7 out of 7 G1: 23 (88%) G2: 23 (92%) G3: 16 (70%) G4: 17 (74%) 95% CI, NR; p: NR Odds ratio for decision aid (G1 & G2) vs. control (G3 & G4)=3.4 95% CI, 1.7 to 6.7; p: NR Mean (95% CI) G1: 7.0 (6 to 7) G2: 7.0 (6 to 7) G3: 7.0 (5 to 7) G4: 7.0 (5 to 7) 95% CI, NR; p: NR
	Patient satisfaction: Acceptable clarity of information (higher scores indicate better satisfaction) Self-report	N (%) responding 6 or 7 of 7 G1: 19 (73%) G2: 13 (52%) G3: 12 (52%) G4: 12 (52%) 95% CI, NR p: NR Odds ratio for decision aid (G1 & G2) vs. control (G3 & G4)=1.6 95% CI, 0.8 to 3.2 p: NR Mean (95% CI) G1: 6.0 (5 to 7) G2: 6.5 (5 to 7) G3: 6.0 (4 to 7) G4: 6.0 (4 to 6) 95% CI, NR p: NR
	Patient satisfaction: Acceptable helpfulness of information (higher scores indicate better satisfaction) Self-report	N (%) responding 6 or 7 of 7 G1: 18 (69%) G2: 12 (48%) G3: 8 (35%) G4: 10 (43%) 95% CI, NR p: NR Odds ratio for decision aid (G1 & G2) vs. control (G3 & G4)=2.3 95% CI, 1.4 to 3.8 p: NR Mean (95% CI) G1: 5.0 (4 to 7) G2: 7.0 (5 to 7) G3: 5.0 (4 to 7) G4: 5.0 (4 to 7) 95% CI, NR p: NR

Table 17. Hyperlipidemia: patient satisfaction (continued)

Author, Year N in Each Group	Outcome	Results
	Patient satisfaction: Would recommend to others deciding on statins. (higher scores indicate better satisfaction) Self-report	N (%) responding 6 or 7 of 7 G1: 21 (84%) G2: 16 (64%) G3: 13 (57%) G4: 11 (50%) 95% CI, NR p: NR Odds ratio for decision aid (G1 & G2) vs. control (G3 & G4)=2.6 95% CI, 0.8 to 8.0 p: NR Mean (95% CI) G1: 6.0 (4 to 7) G2: 7.0 (7 to 7) G3: 5.5 (4 to 7) G4: 6.0 (5 to 7) 95% CI, NR p: NR
	Patient satisfaction: Would prefer similar approach for other treatment choices (higher scores indicate better satisfaction) Self-report	N (%) responding 6 or 7 of 7 G1: 18 (72%) G2: 16 (64%) G3: 14 (61%) G4: 12 (55%) 95% CI, NR p: NR Odds ratio for decision aid (G1 & G2) vs. control (G3 & G4)=1.5 95% CI, 0.6-3.8 p: NR Mean (95% CI) G1: 6.0 (4 to 7) G2: 7.0 (5 to 7) G3: 6.0 (4 to 7) G4: 6.0 (4 to 7) 95% CI, NR p: NR
	Patient satisfaction: Overall acceptability (higher scores indicate better satisfaction) Self-report	N (%) responding 6 or 7 of 7 G1: 20 (77%) G2: 14 (56%) G3: 9 (39%) G4: 10 (43%) 95% CI, NR p: NR Odds ratio for decision aid (G1 & G2) vs. control (G3 & G4)=2.8 95% CI, 1.2-6.9 p: NR Mean (95% CI) G1: 6.0 (4.6 to 6.6) G2: 6.6 (6.0 to 7.0) G3: 5.4 (4.6 to 6.8) G4: 5.4 (4.6 to 6.6) 95% CI, NR p: NR

Abbreviations: CI, confidence interval; G, group; N, number; NR, not reported.

Table 18. Hyperlipidemia: Strength of evidence for interventions with a component of telephone calls

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Hyperlipidemia: telephone calls	3; 13842 (5165)	Medication Adherence, persistence	RCT Medium	Consistent	Direct	Imprecise	Variable measures with variable outcomes Low
	0	Mortality	NA	NA	NA	NA	Insufficient
	0	Morbidity	NA	NA	NA	NA	Insufficient
	0	Quality of life	NA	NA	NA	NA	Insufficient
	0	Patient satisfaction	NA	NA	NA	NA	Insufficient
	0	Health care utilization	NA	NA	NA	NA	Insufficient
	0	Biomarkers	NA	NA	NA	NA	Insufficient
	0	Quality of care	NA	NA	NA	NA	Insufficient

Abbreviations: NA, not applicable; RCT, randomized controlled trial

Table 19. Hyperlipidemia: strength of evidence for interventions delivered primarily by mail

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Hyperlipidemia Delivered primarily by mail	2; 4650 (4246 + NR in 1 study)	Medication Adherence	RCT Medium	Consistent	Indirect	Imprecise	Variable outcomes (Survey, stage of change algorithm, MPR) Low
	0	Mortality	NA	NA	NA	NA	Insufficient
	0	Morbidity	NA	NA	NA	NA	Insufficient
	0	Quality of life	NA	NA	NA	NA	Insufficient
	0	Patient satisfaction	NA	NA	NA	NA	Insufficient
	0	Health care utilization	NA	NA	NA	NA	Insufficient
	0	Biomarkers	NA	NA	NA	NA	Insufficient
	0	Quality of care	NA	NA	NA	NA	Insufficient

Abbreviations: MPR, medication possession ratio; NA, not applicable; NR, not reported; RCT, randomized controlled trial.

Key Question 1. Hypertension: Medication Adherence Interventions

Description of Included Studies

Overview

We found 17 articles comprising 15 randomized controlled trials that evaluated interventions to improve medication adherence in patients taking medications for hypertension.[74, 83, 90, 95, 97-109] Nine studies primarily evaluated patients with a hypertension diagnosis,[98-104, 107-109] one evaluated patients with hypertension and depression,[97] one evaluated patients with diabetes mellitus and hypertension,[90] and four evaluated subgroups with hypertension.[74, 83, 95, 105, 106] We rated 14 studies as having medium risk of bias[74, 83, 90, 95, 97-108] and one study as having low risk of

bias.[109] Table 20 presents an overview of the interventions. Table 21 through Table 25 present results for medication adherence and other outcomes for all studies, followed by strength of evidence tables by type of intervention in Table 26 through Table 28.

Population

All studies were conducted in adults ranging from 18 years or older[108] to 65 years or older[74, 109] with mean ages ranging from 54–55 years old[95] to 78 years old.[74] Women comprised between 0 percent[107] to 75 percent[97] of the study populations. The most commonly reported categories of race and ethnicity were Caucasian and African-American. The prevalence of African-American participants among the studies that reported race and ethnicity ranged from between 8-11 percent[102] up to 70-84.6 percent.[107]

Intervention

All 15 studies evaluated interventions that were targeted at patients. Five studies additionally targeted systems of care[97, 102-104, 107] and one study additionally targeted providers.[103] Five of the 15 studies evaluated interventions with an educational component delivered in part by telephone.[97-102] In three of the five studies, a nurse delivered the intervention by telephone;[98-100, 102] in one study, an interactive computer-based telecommunications system delivered the intervention by telephone;[101] and in the fifth study an integrated care manager delivered the intervention both in person and by telephone.[97] Of the three educational telephone interventions delivered by nurses, two studies provided education about medication adherence and additional educational modules[98-100] and one study provided management of blood pressure medications as guided by home blood pressure readings.[102] Of the remaining studies, five evaluated an intervention that involved face-to-face visits with a pharmacist.[74, 103-107] Two of the pharmacist interventions included components of counseling and education about adherence,[74, 105, 106] two evaluated primary care physician/pharmacist collaborative care for hypertension,[103, 104] and one evaluated the effect of a pharmacist-led hypertension clinic in which pharmacists primarily managed participants' hypertension medications.[107] Two of the five remaining studies delivered and intervention primarily by mail. One evaluated the effect of mailed educational videotape programs about participants' medications and inferred diseases;[95] and the second study evaluated the effect of mailing participants a computer-generated, individualized stage-matched expert system intervention and a manual for antihypertensive adherence based on the transtheoretical model for change.[108] One study evaluated the effect of collaborative care interventions for depression with individualized management using either antidepressant medication or problem-solving treatment on adherence to multiple classes of medications, including angiotensin converting enzyme (ACE)-inhibitors in a subgroup with hypertension.[83] Another study evaluated the effect of involving a patient's social support person in one session of face-to-face nurse-delivered cardiovascular risk education.[90] The final study evaluated the effect of blister-packed medications.[109]

Comparator

Ten of the 15 studies compared active arms to usual care.[83, 95, 97-102, 104, 107, 108] Usual care consisted of no telephone contact in the control group in two studies,[98-100] and no mailings to the control group in one study.[95] Usual care included the typical care delivered within the respective clinic[83, 97, 104] or pharmacy[107] in four studies. Usual care was minimally described in three studies.[101, 102, 108] In one of the remaining five studies, after a 6-month phase in which both

intervention and control groups received an intervention that included blister packing of medications and pharmacist visits, the intervention was discontinued for the control group, which then received medications in pill bottles with a 90-day supply.[74] In another study, the control group had two visits with a pharmacist, one at baseline and one at between 4 and 6 months, with no supplemental services beyond what was customarily offered at each site.[105, 106] In another study involving a face-to-face intervention with a pharmacist, the control group did not have contact with pharmacists but did have contact with study nurses, who measured blood pressures and provided educational information.[103] In a study evaluating the effect of involving a patient's social support person in cardiovascular risk education, the control group did not have involvement of the social support person in the education.[90] In the final study, the control group received medications in pill bottles instead of the blister packs that were provided to the intervention group.[109]

Outcomes and Timing

Medication adherence measures varied widely. None of the studies evaluated initiation or persistence of medication therapy. Self-reported adherence measures included nonvalidated measures in two studies,[103, 104, 107, 108] a stage-of-change algorithm in one study,[108] and Morisky scales in six studies.[90, 98-100, 105, 106] Nonself-report measures included pill counts in two studies,[74, 101] pharmacy refill data in four studies,[83, 95, 107, 109] and the Medication Event Monitoring system (MEMS) caps in two studies.[97, 102] One study used both self-reported (survey questions) and nonself-reported (pharmacy refill data) measures of adherence.[107]

Of the five studies for which we discuss blood pressure outcomes, three reported systolic and diastolic blood pressure measurements (mm Hg) at followup;[74, 97, 105, 106] two reported mean changes (mm Hg) in systolic and diastolic blood pressure between baseline and followup,[101, 102] and one reported the proportion of patients with reductions in systolic and diastolic blood pressure between baseline and followup.[109]

Other outcomes included the occurrence of angina, myocardial infarction, and stroke that were reported in one study.[109] Two studies reported on health care utilization, including emergency department (ED) visits and hospitalizations,[105, 106, 109] with one of the two studies additionally reporting number of contacts with health care providers other than pharmacists.[105, 106] Patient satisfaction and quality-of-life outcomes were reported in one study in the form of answers to nonvalidated survey questions.[105, 106]

The duration of interventions varied among the 15 studies. The shortest intervention lasted 6 weeks[97] and the longest interventions were planned to last 24 months,[98-100] though the publications we identified for both of the 24-month studies reported only 6-month outcomes. In most studies, the adherence outcomes were collected at the conclusion of the intervention. Exceptions included the above-referenced 24-month studies that reported 6-month outcomes,[98-100] one study of an 18-month intervention that reported 6-, 12-, and 18-month outcomes,[108] and a 12-month study that reported 6- and 12-month outcomes.[109] Of note, one study lasted a total of 14 months with an initial 2-month run-in period followed by a 6-month cohort intervention in which both groups received an intervention followed by a final 6-month randomized controlled trial in which one group continued the prior intervention and one group had the intervention discontinued.[74]

Setting

Nine trials focused on primary care populations,[83, 90, 97-100, 102-104, 109] three on pharmacy populations,[74, 105-107], two on health maintenance organization (HMO) populations,[95, 108] and one recruited participants from community sites including senior centers.[101] Of the 115 trials, three were conducted within a population at least partly composed of patients from a Veteran's Administration (VA) Medical Center,[100, 105-107] and one was within a military medical center.[74]

Applicability

Overall, the four studies that were based either within VA Medical Centers or a military hospital were considered to have variable applicability[74, 99, 100, 105-107] due to the unique characteristics of the VA and military populations studied, which were composed of a low proportion of women (ranging from 0 to 22 percent) and a higher proportion of African-American participants (ranging from 32.3 percent to 80–84.6 percent) than studies performed in other settings. In addition, one study performed at a VA medical center was considered to have limited generalizability because a large component of the intervention involved having a pharmacist prescribe medications,[107] which is a role available to pharmacists only within the VA system and a small number of states.

Key Points

Overview

- Medication adherence: Across 15 studies, we found mixed evidence for medication adherence. Seven of the 15 studies reported improvements in medication adherence.
- Morbidity: Six of the seven studies with improved medication adherence reported blood pressure outcomes. We found mixed evidence for improvement in blood pressure outcomes, with four of the six studies reporting improvements in systolic blood pressure, and four of six studies reporting improvements in diastolic blood pressure.
- We graded strength of evidence formally for three intervention groups: (1) those with a component of telephone-delivered education, (2) those that were delivered in person by a pharmacist, and (3) those that were delivered primarily by mail. We judged the body of evidence as insufficient to rate strength of evidence for the interventions that included collaborative depression care, involvement of a patient's social support person in cardiovascular risk education, and blister packaging of medications.

Telephone-Delivered Educational Interventions

- Medication adherence: Among five studies with an educational component delivered in part by telephone, we found mixed evidence for improved medication adherence with overall imprecise outcomes (low strength of evidence). Variable measures were used to assess adherence. Among the two studies that used a Morisky scale, neither study found an improvement in adherence (low strength of evidence). Among the three studies that used objective measures of adherence, including MEMS or pill counts, all three found evidence for improved adherence (moderate strength of evidence).
- Morbidity: The body of evidence showed a mixed magnitude of changes in blood pressure in the intervention groups with mean difference in blood pressure change

between groups ranging from -0.5 to -8.5 mm Hg for systolic blood pressure and -2.1 to -3.1 mm Hg for diastolic blood pressure in two studies (low strength of evidence).
- All other outcomes: We found insufficient strength of evidence as additional outcomes were not reported.

Pharmacist-led Interventions

- Medication adherence: Among five studies involved face-to-face visits with a pharmacist, we found mixed evidence for improved medication adherence with imprecise outcomes with variable measures used to assess medication adherence (low strength of evidence).
- Morbidity: Among the two pharmacist interventions reporting blood pressure outcomes, both reported improved systolic blood pressure in the intervention group with a range of -6.4 to -8.9 mm Hg difference between intervention and control arms at followup (moderate strength of evidence). However, diastolic blood pressure improvements were imprecise without significant improvements in either intervention group; the mean difference between intervention and control arms at followup ranged from -1.1 to -4.4 mm Hg (low strength of evidence).
- Patient satisfaction and quality of life: One study reported patient satisfaction with a variety of measures and found varied, imprecise outcomes (insufficient strength of evidence).
- Healthcare utilization: One study reported healthcare utilization measures and found fewer hospitalizations and visits with providers other than pharmacists in the intervention arm (low strength of evidence) but no difference in ED visits between arms (insufficient evidence).

Mail-based Educational Interventions

- Medication adherence: Among the two larger studies that evaluated mail-based interventions, one found improved medication adherence; variable measures used to assess medication adherence and imprecise outcomes were found (low strength of evidence).
- All other outcomes: We found insufficient strength of evidence because additional outcomes were not reported.

Other Interventions and Outcomes

- We judged the body of evidence as insufficient to rate strength of evidence for the interventions that included collaborative depression care, involvement of a patient's social support person in cardiovascular risk education, and blister packaging of medications.

Detailed Synthesis for Telephone-based Educational Interventions for Hypertension

Medication Adherence

Among the five studies with a component of education delivered in part by telephone,[97-102] three[97, 101, 102] found improved adherence outcomes in the intervention arm (Table 21). The two studies that did not find improved adherence outcomes measured medication adherence with a

Morisky scale at baseline and 6 months.[98-100] Of the three studies that found improved adherence outcomes, two used MEMS caps[97, 102] and one used pill counts to measure adherence.[101] In the two studies that used MEMS caps for adherence measures, one reported the proportion of intervention group participants who were 80 percent or more adherent to hypertension medications (taken: prescribed) as 71.9 percent at 6 weeks,[97] and the other study reported daily adherence or the average proportion of days on which the correct number of doses were taken as prescribed in the intervention group as 80.5 percent at 6 months.[102] The study that used pill counts reported the mean increase in the proportion of medications taken versus prescribed in the intervention arm at 6 months, which was a 2.4 percent mean increase in an unadjusted model and a 17.7 percent mean increase when adjusted for age, sex, baseline medication adherence, and baseline adherence by treatment group. Given the mixed evidence for improved adherence, the variability of measures, and imprecision in outcomes, the overall evidence of improved adherence was graded as low (Table 26). However, when interventions were subdivided by measures of adherence, we found that the two studies that used Morisky scales found no improved adherence and provided low strength of evidence of benefit; we also found that the three studies that used objective adherence measures all found improved adherence in the intervention arms and provided moderate strength of evidence of benefit.

Other Outcomes

Among the five interventions with a component of education delivered by telephone, all three that found improved adherence also reported blood pressure measures (Table 22).[97, 101, 102] Within these three studies, two found improvements in systolic and diastolic blood pressure measures.[97, 102] Outcomes were reported as mean systolic and diastolic blood pressure at followup in one study[97] and as absolute change in systolic and diastolic blood pressure from baseline in the other two studies.[101, 102] The range of change in blood pressure from baseline to followup within the intervention groups was between -11 and -14.2 mm Hg for systolic blood pressure and -5.4 to -6.5 mm Hg for diastolic blood pressure.[101, 102] Differences between intervention and control groups for change in blood pressure from baseline to followup was -0.4 to -8.5 mm Hg for systolic blood pressure and – 2.1 to – 3.1 for diastolic blood pressure for the same two studies. With imprecise changes in blood pressures among the three studies, we found low strength of evidence for improved systolic and diastolic blood pressures among these three studies (Table 26).

Detailed Synthesis for Interventions with Pharmacist Visits for Hypertension

Medication Adherence

In the five studies that included pharmacist visits,[74, 103-107] two found improved medication adherence (Table 21).[74, 105, 106] One of the three studies that did not find improved medication adherence used both pharmacy refill data and survey questions to assess medication adherence.[107] The other two pharmacist studies that did not find improved adherence both used self-reported measures of adherence.[103, 104] Of the two pharmacist studies with improved medication adherence, one used pill counts to report adherence both in the percentage of medication adherence in the intervention arm at 6 months (95.5 percent) and the proportion of participants in the intervention arm with 80 percent or more adherence over 6 months (97.4 percent).[74] The other study with improved adherence reported Morisky scale scores, which

significantly improved in the intervention arm compared with the control arm at the follow-up visit between 4 and 6 months. Within-group Morisky score improvements were also noted in the intervention arm from baseline to followup.[105, 106] Given the mixed findings for improved adherence, measure variability, and outcome imprecision, the evidence of benefit was graded as low Table 27).

Other Outcomes

Among the five pharmacist interventions, both studies that found improved adherence also reported blood pressure measures (Table 22).[74, 105, 106] Both studies also found improvements in systolic blood pressure but did not identify a statistically significant difference in diastolic blood pressure in the intervention group. Both studies reported mean systolic and diastolic blood pressures at followup and one additionally reported differences in systolic and diastolic blood pressures between baseline and followup.[74] Mean systolic blood pressure ranged from 124.4 to 138.5 mm Hg in the intervention groups at followup in these two studies and mean diastolic blood pressure ranged from 67.5 to 80.2 mm Hg. Calculated mean differences between the intervention and control arms at followup ranged from -6.4 to -8.9 mm Hg for systolic blood pressure and -1.1 to -4.4 mm Hg for diastolic blood pressure in these two studies. Since the magnitude of effect was consistent for systolic blood pressure between the two studies and outcomes were precise, the strength of evidence was graded as moderate for this outcome (Table 27). However, because the magnitude of effect was lower for diastolic blood pressure and outcomes were imprecise, the strength of evidence was graded as low for this outcome (Table 27).

Quality of life was evaluated in only one pharmacist intervention study (Table 23).[105, 106] Quality-of-life items included problems with sexual functioning, feeling dizzy upon standing up, and having headaches more than usual, in addition to a number of other items.[105, 106] Only the proportion of intervention patients reporting problems with sexual functioning during the prior 4 weeks changed significantly from baseline to followup (between 4 and 6 weeks), though this proportion was not significantly different between intervention and control groups. Given the varied measures and imprecise outcomes for quality of life, the body of evidence was deemed insufficient for grading strength of evidence (Table 27).

Patient satisfaction was reported in only one pharmacist intervention study (Table 24), and consisted of answers to individual questions from a pharmaceutical care questionnaire.[105, 106] We abstracted only items that directly applied to a patient's experience with medications or the disease for which medications were prescribed. The intervention group scored significantly favorably compared with the control group in questions where they were asked about feeling secure about taking medications, understanding their illness, feeling that the pharmacist took time to make sure that they understood the importance of medications, and feeling that the pharmacist gave complete explanations about their medications.[105, 106] Given the varied measures, limited applicability, and overall imprecise outcomes for patient satisfaction, the body of evidence was deemed insufficient for grading strength of evidence (Table 27).

Health care utilization measures were reported in only one pharmacist intervention study and were ascertained through self-report (Table 25).[105, 106] This study found significantly fewer hospitalizations and fewer contacts with health care providers other than pharmacists over 4 weeks in the intervention arm compared with the control arm but found no difference between groups in mean number of emergency room visits over 4 weeks. Of note, a one-tailed p value of <0.05 was considered a significant result in this study. We graded the strength of evidence

related to hospitalizations and contacts with health care providers other than pharmacists as low and evidence related to emergency room visits as insufficient because of imprecision and a relatively small sample size (Table 27).

Detailed Synthesis for Mail-based Educational Interventions for Hypertension

Medication Adherence

One of the two mail-based interventions found significant improvements in adherence with both a behavioral measure of nonadherence and a stage-of-change assessment for medication adherence at 12 and 18 months but not at 6 months in the intervention arm compared with the control arm (Table 21).[108] The other mail-based study of educational videos did not find improved medication adherence as measured by medication possession ratios in the intervention group compared with the control group among the overall group or among those with a prescription for benezapril or metoprolol (Table 21).[95] Given the mixed findings for improved adherence, measure variability, and outcome imprecision, the evidence of benefit was graded as low (Table 28).

Other Outcomes

The mail-based intervention that found improvements in medication adherence measures did not report blood pressure measures or additional outcome measures.[108]

Detailed Synthesis for Other Interventions for Hypertension

Medication Adherence

The study of a collaborative care model resulting in individualized management of depression care found slightly worsened adherence to oral hypoglycemic medications in the intervention group compared with the control group over 12 months, but did not identify a difference between groups for ACE inhibitor or lipid-lowering agent adherence in subgroup analyses (Table 21).[83] Because this study had imprecise adherence outcomes with small sample sizes, evidence was felt to be insufficient to grade.

The study evaluating the effect of involving a patient's support person in an educational session did not find improved adherence in the intervention groups as measured with the Morisky adherence scale at 12 months.[143] Because this single study had imprecise adherence outcomes, evidence was felt to be insufficient to grade.

In the intervention of medication blister packing, improved adherence was identified in the intervention compared with the control group with pharmacy refill data (Table 21).[109] This study found no difference between treatment arms in the percentage of patients who had prescriptions refilled on time, but did find a significantly higher medication possession ratio (medications received: medications prescribed) in the intervention arm (Table 21). Because this single study had variable adherence outcomes and a small sample size, evidence was felt to be insufficient to grade.

Other Outcomes

The only study that found improved medication adherence and reported blood pressure measures was a study of blister packaging for medications (Table 22).[109] This study did not find

improved absolute systolic or diastolic blood pressures at 6 or 12 months, but did find that a significantly higher proportion of intervention group patients had reduced diastolic blood pressure (but not systolic blood pressure) at 12 months compared with the control group (Table 22).[109] Because this single study had variable, imprecise blood pressure outcomes and a small sample size, evidence was felt to be insufficient to grade. This study additionally reported the occurrence of angina, myocardial infarction, and stroke, which did not differ between groups and was insufficient to grade due to imprecision.[109] This study additionally evaluated health care utilization and found no difference in ED visits and hospitalizations between groups at 6 and 12 months; this outcome was felt to be insufficient to grade due to imprecision (Table 25).[109]

Table 20. Hypertension: study characteristics

Author, Year N at Randomization	Population Setting	Intervention and Comparator
Bogner et al., 2007[97] N=64	Patients ≥50 years Community-based primary care clinic	G1: Integrated care of depression and hypertension; included education, self-management instruction, symptom and side-effects monitoring, referral assistance G2: Usual care
Bosworth et al., 2008[98, 99] N=636	Adults with hypertension Primary care clinics	G1: Nurse-conducted telephone-delivered behavioral/educational intervention based on the Health Decision Model with tailored algorithms and material pertaining to medication adherence and additional modules G2: No nurse telephone contact, no change in care
Bosworth et al., 2005[100] N=588	Adults on medication for hypertension Primary care clinics at VA medical center	G1: Nurse-conducted telephone-delivered behavioral/educational intervention based on the Health Decision Model with tailored and standard information in specific areas using scripts and tailoring algorithms G2: No alterations to usual care other than completing measures at baseline and followup
Carter et al., 2009[103] N=402	Adults over 21 years of age diagnosed with hypertension Community-based family medicine residency programs	G1: Physician/pharmacist collaborative model in which pharmacists addressed suboptimal medication regimens and poor medication adherence and gave feedback to physicians. Study nurses also gave patients educational information and encouraged lifestyle modifications. G2: Patients received Bp measurements at baseline, 3, and 6 months and educational information from nurses. Clinical pharmacists abstained from providing care to patients in control group
Friedman et al., 1996[101] N=299	Adults ≥60 years old on medication for hypertension Community site recruitment	G1: TLC system—an interactive computer-based telecommunications system that converses with patients in their homes between office visits to their physicians to supplement usual care. The system uses computer-controlled speech to ask questions about clinical status and give feedback, education and motivational counseling to the patient to promote adherence to treatments. G2: Regular medical care (not described)
Hunt et al., 2008[104] N=463	Adults with known hypertension Primary care clinics	G1: Collaborative primary care-pharmacist hypertension management. Pharmacists reviewed subjects' medications, vital signs, screened for adverse drug reactions and barriers to adherence, provided education, optimized the antihypertensive regimen, and scheduled follow-up appointments if necessary. G2: Normal schedule of medical care
Johnson et al., 2006[108] N=1227	Adults 18 to 80 years old prescribed hypertension medication Homes of HMO members	G1: A computer-generated, individualized, stage-matched expert system intervention and manual for adherence to antihypertensives based on the transtheoretical model for change. Printed feedback was provided at followup. G2: Did not receive intervention materials

Table 20. Hypertension: study characteristics (continued)

Author, Year N at Randomization	Population Setting	Intervention and Comparator
Lee et al., 2006[74] N=159	Adults ≥65 years old taking ≥4 daily medications, most with hypertension and hyperlipidemia Pharmacy within a U.S. military medical center	G1: Continuation of multicomponent pharmacy-based intervention including clinical pharmacist delivery of individualized medication education every 2 months and blister packing of medications. G2: Discontinuation of intervention, medications provided in pill bottles with a 90-day supply.
Lin et al., 2006[83] N=329	Adults with diabetes mellitus and persistent Depression Primary care clinics	G1: Collaborative care with individualized management of depression care using one of two evidence-based treatments: antidepressant medication or problem-solving treatment G2: Advised to consult primary care physician for depression treatment
Pearce et al., 2005[90] N=199	Adults >21 years old with type 2 diabetes mellitus and poorly controlled hypertension Primary care clinics	G1: One session of in-person nurse-delivered cardiovascular risk education with attendance of patient's social support person followed by mailing of quarterly educational newsletters G2: Same as G1 intervention G3: Same as G1 with exception of not involving patient's social support person for individual patient cardiovascular risk education session
Powell et al., 1995[95] N=4246	Members of a large Midwestern HMO; had a pharmacy claim for benazepril, metoprolol, simvastatin, or transdermal estrogen Homes of HMO members	G1: Subjects mailed one of four educational videotape programs presenting information on the patients' inferred disease/condition process, suggesting behavior changes, how their prescribed drug works, and why adherence is important G2: Received no educational materials
Rudd et al., 2004[102] N=150	Adults eligible for hypertension therapy Primary care clinic	G1: Nurse care management by phone including education and management of blood pressure medications as guided by automated home blood pressure device readings G2: Not described
Schneider et al., 2008[109] N=93	Adults ≥65 years old with a diagnosis of hypertension Primary care clinic	G1: Received lisinopril in a daily-dose adherence package, blister packaged with four rows of seven tablets, with more space for patient information such as what to do if a dose is missed G2: Received lisinopril in traditional bottles of loose tablets
Solomon et al., 1998[105, 106] N=133 (Hypertension) N=98 (COPD)	Hypertension: Adults with hypertension on dihydropyridine or dihydropyridine + diuretic therapy COPD: Adults with COPD currently receiving treatment with at least one inhaler Pharmacies at ten VA medical centers, one university hospital	G1: Pharmaceutical care intervention with five scheduled pharmacist visits over 6 months as well as standardized patient assessment activities and scheduled therapeutic and educational interventions. G2: Two total visits with a pharmacist, one at baseline and the other between 4 and 6 months, no supplemental education or assessment of needs beyond what was customarily offered at each site

Table 20. Hypertension: study characteristics (continued)

Author, Year N at Randomization	Population Setting	Intervention and Comparator
Vivian et al., 2002[107] N=56	Adults >18 years old on medication for hypertension Pharmacy at VA medical center	G1: Clinical pharmacist intervention including monthly visits to pharmacist-managed hypertension clinic for hypertension medication adjustment, drug counseling, and compliance assessment G2: Received traditional pharmacy services, no visits to pharmacist-managed hypertension clinic

Abbreviations: Bp, blood pressure; COPD, chronic obstructive pulmonary disease; G, group; HMO, health maintenance organization; N, number TLC, telephone-linked computer; US, United States; VA, Veterans' Administration.

Table 21. Hypertension: medication adherence

Study N Analyzed for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
Bogner et al. 2007[97] G1: 32 G2: 32	Adherent to antidepressants Dichotomous outcome of adherence (taken: prescribed) (≥80%) MEMS	From baseline to 6 weeks: G1: 23 (71.9%) G2: 10 (31.3%) p: .001
G1: 32 G2: 32	Adherent to hypertension medications Dichotomous outcome of adherence (taken: prescribed) (≥80%) MEMS	From baseline to 6 weeks: G1: 25 (78.1) G2: 10 (31.3) p: <.001
Bosworth et al., 2008[98] G1: 319 G2: 317	Increase in proportion of self-reported adherence from baseline to 6 months on 4-item Morisky scale Self-report	G1: 9% (increase from 63% to 72%) G2: 1% (increase from 67% to 68%) 95% CI, NR p: NR
Bosworth et al., 2005[100] G1: NR G2: NR	Change in overall proportion reporting medication adherence at 6 months on 4-item Morisky scale; difference between G1 and G2 Self-report	0.74% 95% CI, -6.2, 7.6 p: NR
G1: NR G2: NR	Among those reporting adherence at baseline: Proportion reporting adherence at 6 months on 4-item Morisky scale Self-report	G1: 83% G2: 85% 95% CI, NR p: 0.68
G1: NR G2: NR	Among those reporting nonadherence at baseline: Proportion reporting adherence at 6 months on 4-item Morisky scale Self-report	G1: 46% G2: 34% 95% CI, NR p: 0.08
Carter et al., 2009[103] G1: 192 G2: 210 G1: 192 G2: 210	Percentage of patients with low medication adherence on Morisky scale (defined by answering "yes" to ≥3 of 5 questions) Self-report	Baseline (Mean %, SD) G1: 17.3% (27.5) G2: 18.7% (22.0) 95% CI, NR 6 month followup (Mean %, SD) G1: 14.6% (25.4) G2: 14.7% (20.9) 95% CI, NR G1: p (within-group): 0.979 G2: p (within-group): 0.602

Table 21. Hypertension: medication adherence (continued)

Study N Analyzed for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
Friedman et al., 1996[101] G1: 133 G2: 134	Antihypertensive medication adherence: Proportion of total number of doses taken divided by the number that should have been taken by each subject Pill count	Change in proportion taken from baseline to 6 months: Unadjusted change from baseline G1: 2.4% mean increase G2: 0.4% mean increase p=0.29 Adjusted* change from baseline G1: 17.7% mean increase G2: 11.7% mean increase p=0.03 * Adjusted for age, sex, baseline medication adherence, and baseline adherence by treatment group
Overall N: 26 G1: NR G2: NR	Antihypertensive medication adherence among nonadherent subjects at baseline (taking <80% of medications): Proportion of total number of doses taken divided by the number that should have been taken by each subject Pill count	Adjusted* change from baseline G1: 36.0% mean increase G2: 26.0% mean increase p=0.03 * Adjusted for age, sex, baseline medication adherence, and baseline adherence by treatment group
Overall N: 241 G1: NR G2: NR	Antihypertensive medication adherence: Among adherent subjects at baseline (taking ≥80% of medications) Proportion of total number of doses taken divided by the number that should have been taken by each subject Pill count	Adjusted* change from baseline G1: 0.6 mean increase G2: 3.0 mean increase p=0.69 * Adjusted for age, sex, baseline medication adherence, and baseline adherence by treatment group
Hunt et al., 2008[104] G1: 142 G2: 130	Proportion of subjects reporting high medication adherence on Morisky scale at study end Self-report	G1: 67% (N=95/142) G2: 69% (N=90/130) 95% CI, NR p: 0.771
G1: 142 G2: 130	Increase in adherence on Morisky scale from baseline to final assessment Self-report	G1: 61% at baseline, 67% at end point, p=0.08 for within-group comparison G2: no significant increase from baseline to final (p=0.52) [baseline and end point % not reported] 95% CI, NR p: NR between groups
Johnson et al., 2006[108] G1: Not Reported G2: Not Reported	Behavioral measure of nonadherence: 5-item survey with lower score indicating better adherence Self-report	Baseline: no significant difference, no numbers reported, in figure only; 95% CI, NR p >0.05 6 months: no significant difference, no numbers reported, in figure only; 95% CI, NR p >0.05 12 months: G1 with significantly lower score, no numbers reported, in figure only; 95% CI, NR p<0.01

Table 21. Hypertension: medication adherence (continued)

Study N Analyzed for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
		18 months: G1 with significantly lower score, no numbers reported, in figure only; 95% CI, NR p<0.001
G1: NR G2: NR	In pre-action portion of sample: Proportion reaching Action or Maintenance stage for medication adherence on stage of change algorithm Results ranged as follows: Precontemplative (not intending to become adherent), Contemplative (intending to become adherent in the next 6 months), Preparation (intending to become adherent in the next 30 days), Action (having improved adherence for <6 months), and Maintenance (having improved adherence for >6 months) Self-report	Baseline: no significant difference, no numbers reported, in figure only; 95% CI, NR p >0.05 6 months: no significant difference, no numbers reported, in figure only; 95% CI, NR p >0.05 12 months: G1: 73.1% G2: 57.6% 95% CI, NR p<0.001 18 months: G1: 69.1% G2: 59.2% 95% CI, NR p<0.01
Lee et al., 2006[74] G1: 83 G2: 76	Percentage medication adherence for 6 months (proportion of pills taken), mean (SD) Pill count	G1: 95.5% (7.7) G2: 69.1% (16.4) 95% CI, NR p<0.001
G1: 83 G2: 76	Proportion of participants with ≥ 80% adherence to all medications over 6 months Pill count	G1: 97.4% G2: 21.7% 95% CI, NR p<0.001
Lin et al., 2006[83] G1: 103 G2: 103	Percentage of days nonadherent to medication at 12 months Pharmacy refill data	Oral hypoglycemic agent Baseline (%) (Mean (SD)) G1: 19.8% (21.3%) G2: 22.9% (24.0%) 95% CI, NR p: NS Over 12 months (%) (Mean (SD))
G1: 103 G2: 103		G1: 28.2% (28.9%) G2: 24.0% (24.7%) 95% CI, NR p: <0.03 ACE inhibitor
G1: 54 G2: 65		Baseline (%) (Mean (SD)) G1: 27.4% (27.1%) G2: 29.7% (29.3%) 95% CI, NR p: NS
G1: 59 G2: 52		Over 12 months (%) (Mean (SD)) G1: 24.2% (22.7%) G2: 18.9% (17.4%) 95% CI, NR p: NS

Table 21. Hypertension: medication adherence (continued)

Study N Analyzed for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
G1: 50 G2: 52		Lipid-lowering agent Baseline (%) (Mean (SD)) G1: 29.3% (26.7%) G2: 24.5% (23.0%) 95% CI, NR p: NS
G1: 54 G2: 63		Over 12 months (%) (Mean (SD)) G1: 28.8% (27.1%) G2: 27.7% (24.0%) 95% CI, NR p: NS
G1: 103 G2: 103	Adjusted mean difference in percentage of days nonadherent comparing G1 and G2 over 12 months Pharmacy refill data	Oral hypoglycemic agent (%)=-6.3% 95% CI, -11.91 to -0.71 p: <0.03
G1: 59 G2: 52		ACE inhibitor (%)=-2.5% 95% CI, -8.69 to 3.70 p: NS
G1: 54 G2: 63		Lipid-lowering agent (%)=-0.2% 95% CI, -7.23 to 6.76 p: NS
Pearce et al., 2005[90] G1: 50 G2: 58 G3: 91	Level of adherence (low, medium, or high) measured by Morisky Adherence Scale at baseline and 12 months followup Self-report	<u>Baseline</u> High (%): G1=50.0 G2=29.8 G3=41.8 Medium (%): G1=42.0 G2=63.2 G3=49.5 Low (%): G1=8.0 G2=7.0 G3=8.8 95% CI, NR p (G1 vs. G2 vs. G3): 0.1584 p (G1 + G2 vs. G3): 0.4358 <u>12 months</u> High (%): G1=NR G2=NR G3=NR Medium (%): G1=NR G2=NR G3=NR Low (%): G1=NR G2=NR G3=NR p: NS

Table 21. Hypertension: medication adherence (continued)

Study N Analyzed for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
Powell et al., 1995[95]	MPR	Over a 9-month period:
N=4246	Pharmacy refill data	Overall (Mean (SD))
G1: 1993		G1: 0.70 (0.23)
G2: 2253		G2: 0.70 (0.28)
		95% CI, NR
		p: NR
G1: 175		Benazepril (Mean (SD))
G2: 243		G1: 0.71 (0.25)
		G2: 0.72 (0.26)
		95% CI, NR
		p: NR
G1: 717		Transdermal estrogen (Mean (SD))
G2: 823		G1: 0.60 (0.32)
		G2: 0.58 (0.32)
		95% CI, NR
		p: NR
G1: 830		Metoprolol (Mean (SD))
G2: 898		G1: 0.74 (0.27)
		G2: 0.73 (0.28)
		95% CI, NR
		p: NR
G1: 271		Simvastatin (Mean (SD))
G2: 297		G1: 0.73 (0.26)
		G2: 0.70 (0.28)
		95% CI, NR
		p: NR
G1: 1993	Compliance (MPR $\geq$ 0.80)	Over a 9-month period:
G2: 2253	Pharmacy refill data	Overall (N (%))
		G1: 917 (46%)
		G2: 998 (44%)
		95% CI, NR
		p: NR
G1: 175		Benazepril (N (%))
G2: 243		G1: 78 (45%)
		G2: 104 (44%)
		95% CI, NR
		p: NR
G1: 717		Transdermal estrogen (N (%))
G2: 823		G1: 266 (37%)
		G2: 209 (35%)
		95% CI, NR
		p: NR
G1: 830		Metoprolol (N (%))
G2: 898		G1: 438 (53%)
		G2: 466 (52%)
		95% CI, NR
		p: NR
G1: 271		Simvastatin (N (%))
G2: 297		G1: 135 (50%)
		G2: 138 (46%)
		95% CI, NR
		p: NR

Table 21. Hypertension: medication adherence (continued)

Study N Analyzed for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
Rudd et al., 2004[102] G1: NR G2: NR	Daily adherence at 6 months (average proportion of days on which correct number of doses taken as prescribed) MEMS	G1: 80.5% (23.0 SD) G2: 69.2% (31.1 SD) 95% CI, NR p=0.03
G1: NR G2: NR	Among those with once-daily medication dosing: Daily adherence at 6 months (average proportion of days on which correct number of doses taken as prescribed) MEMS	G1: 82% (28 SD) G2: 75% (27 SD) 95% CI, NR p not reported, not significant per text
G1: NR G2: NR	Among those with twice-daily or more frequent medication dosing: Daily adherence at 6 months (average proportion of days correct number of doses taken) MEMS	G1: 69% (34 SD) G2: 49% (41 SD) 95% CI, NR p not reported, not significant per text
Schneider et al., 2008[109] G1: 47 G2: 38	Percentage of patients who had prescriptions refilled on time (±5 days of due date) Pharmacy refill data	Mean (SD) G1: 80.4% (21.2) G2: 66.1% (28.0) 95% CI, NR p: 0.12
G1: 47 G2: 38	Medication possession ratio (sum of day's supply for all Rxs received during the study divided by the number of days between the dates of the first and last Rx dispensing) Pharmacy refill data	Mean (SD) G1: 0.93 (11.4) G2: 0.87 (14.2) 95% CI, p: 0.039
Solomon et al., 1998[105, 106] G1: 62 G2: 70	Hypertension arm: Reporting compliance at baseline on 4-point Morisky scale, with lower score reflecting better compliance Self-report	G1: 0.63 (SD 0.111) G2: 0.60 (SD 0.087) 95% CI, NR p: 0.75
G1: 62 G2: 70	Hypertension arm: Reporting compliance at visit between 4 and 6 months on 4-point Morisky scale, with lower score reflecting better compliance Self-report	G1: 0.23 (SD 0.054) G2: 0.61 (SD 0.094) 95% CI, NR p: 0.007
G1: 62 G2: 70	Hypertension arm: Reporting compliance comparing baseline and 4-6-month scores on 4-point Morisky scale, with lower score reflecting better compliance Self-report	G1 (baseline): 0.63 (SD 0.111) G1 (4-6 months): 0.23 (SD 0.054) 95% CI, NR p<0.05 G2 (baseline): G2: 0.60 (SD 0.087) G2 (4-6 months): G2: 0.61 (SD 0.094) 95% CI, NR p: NR
Vivian et al., 2002[107] G1: 26 G2: 27	Compliance Survey question at 6 months: “How often do you forget to take your medication?”; proportion answering ≥1 time a week Self-report	G1: 68% G2: 48% 95% CI, NR p: 0.252
G1: 26 G2: 27	Compliance Survey question at 6 months: “How often do you stop taking your medication when you are feeling better?” proportion answering ≥1 time a week	G1: 32% G2: 20% 95% CI, NR p: 0.520

Table 21. Hypertension: medication adherence (continued)

Study N Analyzed for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
G1: 26 G2: 27	Compliance Survey question at 6 months: "How often do you stop taking your medication when you think it is making you feel worse?"; proportion answering ≥1 time a week Self-report	G1: 40% G2: 20% 95% CI, NR p: 0.217
G1: 26 G2: 27	Compliance Survey question at 6 months: "When your medication does not seem to be working, how often do you take more than your health care provider prescribed?"; proportion answering ≥1 time a week Self-report	G1: 8% G2: 8% 95% CI, NR p: 1.00
G1: 26 G2: 27	Compliance Survey question at 6 months: "If you answered yes to being away from home overnight in the last 3 months, did you forget to take your medication when you were away from home overnight?"; proportion who answered sometimes (2-3 times/week) and always (>3 times/week) Self-report	G1: 15% G2: 10% 95% CI, NR p: 1.00
G1: 26 G2: 27	Proportion that received refills for antihypertensive agents within 2 weeks of the next scheduled refill date Pharmacy refill data	G1: 85% G2: 93% 95% CI, NR p >0.42

Abbreviations: ACE, angiotensin converting enzyme; CI, confidence interval; G, group; MEMS, medication event monitoring system; MPR, medication possession ratio; NR, not reported; NS, not significant; rxs, prescriptions; SD, standard deviation.

Table 22. Hypertension: morbidity

Author, Year N in Each Group	Outcome	Results
Bogner et al. 2007[97] G1: 32 G2: 32	Depression severity Center for Epidemiologic Studies-Depression Scale (range of score 0 to 60 with higher scores indicating more depression symptoms)	Score at 6 weeks: G1: 9.9 (10.7) G2: 19.3 (15.2) p: 0.006
G1: 32 G2: 32	Systolic blood pressure (mm Hg) Automated Bp monitor	Mean (SD) at 6 weeks: G1: 127.3 mm Hg (17.7) G2: 141.3 mm Hg (18.8) p: 0.003
G1: 32 G2: 32	Diastolic blood pressure (mm Hg) Automated Bp monitor	Mean (SD) at 6 weeks: G1: 75.8 mm Hg (10.7) G2: 85.0 mm Hg (11.9) p: 0.002
Friedman et al., 1996[101] G1: 133 G2: 134	Systolic blood pressure (mm Hg) change from baseline to 6 months Measured by field technicians	G1: 11 mm Hg (mean decrease) G2: 10.6 mm Hg (mean decrease) 95% CI, NR p: 0.85
G1: 133 G2: 134	Diastolic blood pressure (mm Hg) change from baseline to 6 months Measured by field technicians	G1: 5.4 mm Hg (mean decrease) G2: 3.3 mm Hg (mean decrease) 95% CI, NR p: 0.09
Lee et al., 2006[74] G1: 64 G2: 57	Among patients with drug-treated hyperlipidemia: LDL-C at 14 months Direct assay measurement	G1: 87.5 mean (SD 24.2) G2: 88.4 mean (SD 21.0) p=0.84
G1: 64 G2: 57	Among patients with drug-treated hyperlipidemia: difference between LDL-C at 2 months and 14 months Direct assay measurement	G1: -2.8 (95% CI, -8.1, 2.5) G2: -5.8 (95% CI, -11.0, 0.6) p=0.85
G1: 73 G2: 62	Among patients with drug-treated hypertension: systolic blood pressure at 14 months (6-month RCT outcome) Measured by pharmacist	G1: 124.4 mm Hg (SD 14.0) G2: 133.3 mm Hg (SD 21.5) p=0.005
G1: 73 G2: 62	Among patients with drug-treated hypertension: difference between systolic blood pressure measures at 2 months and 14 months (6-month cohort + 6-month RCT outcome) Measured by pharmacist	G1: -6.9 mm Hg (95% CI, -10.7, -3.1) G2: -1.0 mm Hg (95% CI, -5.9, 3.9) p=0.04
G1: 73 G2: 62	Among patients with drug-treated hypertension: diastolic blood pressure at 14 months (6-month cohort + 6-month RCT outcome) Measured by pharmacist	G1: 67.5 mm Hg (SD 9.9) G2: 68.6 mm Hg (SD 10.5) p=0.54
G1: 73 G2: 62	Among patients with drug-treated hypertension: difference between diastolic blood pressure measures at 2 months and 14 months (6-month cohort + 6-month RCT outcome) Measured by pharmacist	G1: -2.5 mm Hg (SD -4.9 to -0.2) G2: -1.2 mm Hg (SD -3.7 to 1.2) p=0.39

Table 22. Hypertension: morbidity (continued)

Author, Year N in Each Group	Outcome	Results
Rudd, et al., 2004[102] G1: 74 G2: 76 G1: 74 G2: 76	Change in systolic blood pressure between baseline and 6 months Measured by blinded study personnel Change in diastolic blood pressure between baseline and 6 months Measured by blinded study personnel	G1: -14.2 mm Hg (95% CI, -18.2 to -10.0) G2: -5.7 mm Hg (95% CI, -10.2 to -1.3) p<0.01 G1: -6.5 mm Hg (95% CI, -8.8 to -4.1) G2: -3.4 mm Hg (95% CI, -5.3 to -1.5) p<0.05
Schneider et al., 2008[109] G1: 47 G2: 38	Absolute change in systolic blood pressure (from baseline) Medical chart review	Mean (SD) absolute change in mm Hg: 6 months G1: -4.2 (21.5) G2: -4.2 (20.9) 95% CI, NR p: 0.992 12 months G1: -2.7 (16.5) G2: -1.3 (17.8) 95% CI, NR p: 0.669
G1: 47 G2: 38	Absolute change in diastolic blood pressure (from baseline) Medical chart review	Mean (SD) absolute change in mm Hg: 6 months G1: -0.8 (12.4) G2: 1.8 (9.1) 95% CI, NR p: 0.287 12 months G1: -3.0 (11.6) G2: 2.7 (10.7) 95% CI, NR p: 0.125
G1: 47 G2: 38	Proportion of patients with reduced systolic blood pressure Medical chart review	At 6 months: G1: 48.9% G2: 62.9% p: 0.213 At 12 months: G1: 46.0% G2: 40.9% p: 0.312
G1: 47 G2: 38	Proportion of patients with reduced diastolic blood pressure Medical chart review	At 6 months: G1: 46.7 G2: 37.1 p: 0.393 At 12 months: G1: 48.0 G2: 18.2 p=0.031
G1: 47 G2: 38	Occurrence of angina Medical chart review	G1: NR G2: NR 95% CI, NR p: NR Numbers not reported, but results were not significant
G1: 47 G2: 38	Occurrence of MI Medical chart review	G1: NR G2: NR 95% CI, NR p: NR Numbers not reported, but results were not significant

Table 22. Hypertension: morbidity (continued)

Author, Year N in Each Group	Outcome	Results
G1: 47 G2: 38	Occurrence of stroke Medical chart review	G1: NR G2: NR 95% CI, NR p: NR Numbers not reported, but results were not significant
Solomon et al., 1998[105, 106] G1: 63 G2: 70	Hypertension group: First systolic Bp taken at visit Measured by pharmacist	Visit 1 (baseline G1: 146.7 mm Hg (16.8 SD) G2: 146.2 mm Hg (17.0 SD) 95% CI, NR p: NR Visit 5 (between 4 and 6 weeks) G1: 138.5 mm Hg (13.9 SD) G2: 144.9 mm Hg (21.3 SD) 95% CI, NR p: 0.044
G1: 63 G2: 70	Hypertension group: Within-group comparison of first systolic Bp taken at Visit 1 (baseline) and Visit 5 (between 4 and 6 weeks) Measured by pharmacist	G1 (Visit 1): 146.7 (16.8 SD) G1 (Visit 5): 138.5 (13.9 SD) 95% CI, NR p<0.01 G2 (Visit 1): 146.2 (17.0 SD) G2 (Visit 5): 144.9 (21.3 SD) 95% CI, NR p: NR
G1: 63 G2: 70	Hypertension group: First diastolic Bp taken at Visit 1 (baseline) Measured by pharmacist	G1: 84.6 mm Hg (13.2 SD) G2: 87.0 mm Hg (10.9 SD) 95% CI, NR p: NR
G1: 63 G2: 70	Hypertension group: First diastolic Bp taken at Visit 5 (between 4 and 6 weeks) Measured by pharmacist	G1: 80.2 mm Hg (9.6 SD) G2: 83.2 mm Hg (11.5 SD) 95% CI, NR p: NR
G1: 63 G2: 70	Hypertension group: Within-group comparison of first diastolic Bp taken at Visit 1 (baseline) and Visit 5 (between 4 and 6 weeks) Measured by pharmacist	G1 (Visit 1): 84.6 mm Hg (13.2 SD) G1 (Visit 5): 80.2 mm Hg (9.6 SD) 95% CI, NR p: NR G2 (Visit 1): 87.0 mm Hg (10.9 SD) G2 (Visit 5): 83.2 mm Hg (11.5 SD) 95% CI, NR p: NR

Abbreviations: Bp, blood pressure; CI, confidence interval; G, group; mm Hg, millimeters of mercury; LDL-C, low density lipoprotein cholesterol; mm, millimeter; NR, not reported; RCT, randomized controlled trial; SD, standard deviation.

Table 23. Hypertension: quality of life

Author, Year N in Each Group	Outcome	Results
Solomon et al., 1998[105, 106] G1: NR G2: NR	Hypertension group: Proportion of participants reporting problems with sexual functioning during previous 4 weeks - From Lipid Form 5.1 developed by the Health Outcomes Institute Self-report	Visit 1 (baseline) G1: 22 (34.0%) G2: 19 (26.0%) 95% CI, NR p: NR Visit 5 (between 4 and 6 weeks) G1: 8 (2.5%) G2: 8 (25.0%) 95% CI, NR p: NR
G1: NR G2: NR	Hypertension group: Participants reporting problems with sexual functioning during previous 4 weeks, within-group comparison - From Lipid Form 5.1 developed by the Health Outcomes Institute Self-report	G1 (baseline): 22 (34.0%) G1 (between 4 and 6 weeks): 8 (2.5%) 95% CI, NR p: 0.003 G2 (baseline): 19 (26.0%) G2 (between 4 and 6 weeks): 8 (25.0%) 95% CI, NR p: NR
G1: NR G2: NR	Hypertension group: "Feeling dizzy upon standing up," mean score on Likert scale of 1 (never) to 5 (very often) - From Lipid Form 5.1 developed by the Health Outcomes Institute Self-report	Visit 1 (baseline) G1: 1.7 (1.1 SD) G2: 2.0 (1.1 SD) 95% CI, NR p: NR Visit 5 (between 4 and 6 weeks) G1: 1.4 (0.8 SD) G2:1.4 (0.8 SD) 95% CI, NR p: NR
G1: NR G2: NR	Hypertension group: “Headaches more than usual,” mean score on a Likert scale of 1 (never) to 5 (very often) - From Lipid Form 5.1 developed by the Health Outcomes Institute Self-report	Visit 1 (baseline) G1: 1.5 (1.0) G2: 1.6 (1.2) 95% CI, NR p: NR Visit 5 (between 4 and 6 weeks) G1: 1.2 (0.8) G2:1.2 (0.8) 95% CI, NR p: NR

Abbreviations: CI, confidence interval; G, group; NR, not reported; SD, standard deviation.

Table 24. Hypertension: patient satisfaction

Author, Year N in Each Group	Outcome	Results: Mean (SD)
Solomon et al., 1998[105, 106] G1: 62 G2: 68	Answer to PCQ that intervention: "Makes me feel secure about taking my medications" - Likert scale of 1 (strongly agree) to 5 (strongly disagree) Self-report	G1: 1.39 (0.49) G2: 1.69 (0.68) 95% CI, NR p: 0.004
G1: 62 G2: 68	Answer to PCQ that intervention: “Helps me understand my illness" - Likert scale of 1 (strongly agree) to 5 (strongly disagree) Self-report	G1:1.45 (0.59) G2: 1.84 (0.77) 95% CI, NR p: 0.002
G1: 62 G2: 68	Answer to PCQ that pharmacist: "Does not take time to make sure I understand the importance of my medications" - Likert scale of 1 (strongly agree) to 5 (strongly disagree) Self-report	G1: 4.21 (1.03) G2: 3.88 (1.08) 95% CI, NR p: 0.079
G1: 62 G2: 68	Answer to PCQ that pharmacist: "Gives complete explanations about my medications" - Likert scale of 1 (strongly agree) to 5 (strongly disagree) Self-report	G1: 1.48 (0.54) G2: 1.82 (0.80) 95% CI, NR p: 0.006
G1: 62 G2: 68	Answer to PCQ item 6 that pharmacist: “Should give more complete explanation about my medications" - Likert scale of 1 (strongly agree) to 5 (strongly disagree) Self-report	G1 4.16 (0.93) G2 3.81 (1.03) 95% CI, NR p=0.042

Abbreviations: CI, confidence interval; G, group; NR, not reported; PCQ, Pharmaceutical Care Questionnaire.

Table 25. Hypertension: health care utilization

Author, Year N in Each Group	Outcome	Results
Schneider et al., 2008[109] G1: 47 G2: 38	Emergency department visits and hospitalizations at 6 and 12 months (for prior 6-month period) Medical chart review	G1: NR G2: NR 95% CI, NR p: NR Numbers not reported, but results were not significant
Solomon et al., 1998[105, 106] G1: 63 G2: 61	Hypertension group: Mean number of Emergency Room visits in 4 weeks prior - at 4-6 week visit Self-report	G1: 0.05 (0.22 SD) G2: 0.13 (0.39 SD) 95% CI, NR p: NR
G1: 63 G2: 61	Hypertension group: Mean number of hospitalizations in 4 weeks prior—at 4-6 week visit Self-report	G1: 0.02 (0.13 SD) G2: 0.10 (0.35 SD) 95% CI, NR p<0.05 (one-tailed)
G1: 63 G2: 61	Hypertension group: contacts with "other health care providers" (MD, NP, PA or RN) in 4 weeks prior—at 4-6 week visit Self-report	G1: 0.59 (0.78 SD) G2: 1.0 (0.82 SD) 95% CI, NR p: <0.05 (one-tailed)

Abbreviations: CI, confidence interval; G, group; NR, not reported; SD, standard deviation.

Table 26. Hypertension: strength of evidence for interventions with a component of telephone-delivered education

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Hypertension Telephone-based education	5; 1737 (967 + NR in 2 studies)	Medication Adherence, overall (all measures)	RCT Medium	Consistent	Direct	Imprecise	Multiple variable outcomes (Morisky, MEMS and pill count) Low
	2; 1224 (636 + NR in 1 study)	Medication adherence, Morisky	RCT Medium	Consistent	Direct	Imprecise	No statistically significant improvement Low
	3; 513 (331 + NR in 1 study)	Medication adherence, MEMS or pill count	RCT Medium	Consistent	Direct	Precise	Multiple outcomes Moderate
	0	Biomarkers	NA	NA	NA	NA	Insufficient
	0	Mortality	NA	NA	NA	NA	Insufficient
	3; 513 (481)	SBP	RCT Medium	Consistent	Direct	Imprecise	- 14.0 mm Hg mean SBP difference (G1 vs. G2) in 1 study - 0.5 to - 8.5 mm Hg mean difference (G1 vs. G2) in SBP change from baseline to 6 months in 2 studies Low
	3; 513 (481)	DBP	RCT Medium	Consistent	Direct	Imprecise	- 9.2 mm Hg mean difference (G1 vs. G2) in 1 study - 2.1 to - 3.1 mm Hg mean difference (G1 vs. G2) in SBP change from baseline to 6 months in 2 studies Low
	0	Quality of life	NA	NA	NA	NA	Insufficient
	0	Patient satisfaction	NA	NA	NA	NA	Insufficient
	0	Healthcare utilization	NA	NA	NA	NA	Insufficient
	0	Quality of care	NA	NA	NA	NA	Insufficient

Abbreviations: DBP, diastolic blood pressure; G, group; MEMS, Medication Event Monitoring System; mm Hg, millimeter mercury; NA, not applicable; NR, not reported; RCT, randomized controlled trial; s diff, significant difference; SBP, systolic blood pressure; sig, significant.

Table 27. Hypertension: strength of evidence for interventions delivered face-to-face by pharmacist

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Hypertension Pharmacist face-to-face	5; 1213 (1018)	Medication Adherence	RCT Medium	Consistent	Direct	Imprecise	Multiple variable outcomes (Morisky, pill count, pharmacy refill, self-report) Low
	0	Biomarkers	NA	NA	NA	NA	Insufficient
	0	Mortality	NA	NA	NA	NA	Insufficient
	2; 292 (267)	SBP	RCT Medium	Consistent	Direct	Precise	-6.4 to -8.9 mm Hg mean SBP difference (G1 vs. G2) in 2 studies Moderate
	2; 292 (267)	DBP	RCT Medium	Consistent	Direct	Imprecise	-1.1 to -4.4 mm Hg mean DBP difference (G1 vs. G2) in 2 studies Low
	1, 133 (132)	Quality of life	RCT Medium	Unknown	Indirect	Imprecise	Various measures with varied outcomes Insufficient
	1; 133 (132)	Patient satisfaction	RCT Medium	Unknown	Indirect	Imprecise	Various measures with varied outcomes Insufficient
	1; 133 (124)	Health care utilization: ER visits, hospital-lizations and contacts with health care providers	RCT Medium	Unknown	Direct	Imprecise	Varied measures, variable magnitude ER visits: Insufficient Hospital visits: Low Other contacts: Low
	0	Quality of care	NA	NA	NA	NA	Insufficient

Abbreviations: DBP, diastolic blood pressure; G, group; Hosp, hospital; intvn, intervention; mm, millimeter; NA, not applicable; RCT, randomized controlled trial; S diff, significant difference; SBP, systolic blood pressure; sig, significant.

Table 28. Hypertension: strength of evidence for interventions delivered primarily by mail

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Hypertension Delivered primarily by mail	2; 5473 (4246 + NR in 1 study)	Medication Adherence	RCT Medium	Consistent	Indirect	Imprecise	Variable outcomes (survey, stage of change algorithm, MPR) Low
	0	Biomarkers	NA	NA	NA	NA	Insufficient
	0	Mortality	NA	NA	NA	NA	Insufficient
	0	Morbidity	NA	NA	NA	NA	Insufficient
	0	Quality of life	NA	NA	NA	NA	Insufficient
	0	Patient satisfaction	NA	NA	NA	NA	Insufficient
	0	Health care utilization	NA	NA	NA	NA	Insufficient
	0	Quality of care	NA	NA	NA	NA	Insufficient

Abbreviations: NA, not applicable; MPR, medication possession ratio; NR, not reported; RCT, randomized controlled trial.

Key Question 1. Heart Failure: Medication Adherence Interventions

Description of Included Studies

Overview

We identified four studies that evaluated interventions to improve medication adherence among patients with heart failure.[110-113] We rated three studies as having medium risk of bias[110, 112, 113] and one study as having low risk of bias.[111] Table 29 presents an overview of the interventions. Table 30 through Table 35 present results for medication adherence and other outcomes (medication adherence, mortality, quality of life, patient satisfaction, health care utilization, and costs) for all studies, followed by strength of evidence tables by type of intervention (Table 36 through Table 38).

Population

All studies were conducted in adults ranging from ages 18 and older[113] to ages 70 and older[112] with participant ages ranging from a mean of 55–57 years old[113] to a median age of 80 years old.[112] Women comprised between 20–26 percent[113] and 66–68 percent[111, 112] of the study populations. The most commonly reported categories of race and ethnicity were Caucasian and African-American. African-American participants comprised between 23–33 percent[110] and 45–52 percent[111] of the study population in the two studies that reported this information.

Intervention

The four studies evaluated diverse interventions all targeted at patients; three studies additionally targeted systems of care (Table 29).[111-113] One study included two intervention arms and one control arm.[110] In this study with two intervention arms, video calls were delivered via provided equipment to the first intervention arm and telephone calls were delivered to the second intervention arm; a research assistant made video and telephone calls to remind participants to take their medications daily.[110] Another study evaluated a pharmacist-led intervention that provided participants with verbal instructions, literacy-sensitive written materials, and labeling of

medications with icons to promote adherence.[111] The third study examined a multidisciplinary, multisetting intervention with the following components: as inpatients, patients partook in nurse-delivered education that focused on adherence, visits from a dietician and social worker, and medication review by a geriatric cardiologist; following discharge, homecare services visited patients at home and the study nurse telephoned patients.[112] The final study evaluated an intervention in which patients were given access to their online medical record, an online educational guide for heart failure, and a messaging system to communicate with nursing staff.[113]

Comparator

Active arms were compared with usual care in all four studies. In the study of video and phone call reminders, no calls were made to the control group.[110] In the pharmacist-led intervention, the control group had no contact with the intervention pharmacist beyond an initial visit to obtain medication history.[111] In the multidisciplinary, multisetting study, the control group received conventional care from their regular physician with standard hospital and discharge services.[112] In the final study of access to online medical records, the control group had no access to online records and received the same educational guide for heart failure as the intervention arm; however, the educational guide was provided as a printed packet instead of as an online document.[113]

Outcomes

None of the studies reported on persistence or initiation of medication. Measures of adherence included the Medication Event Monitoring System (MEMS) caps in two studies,[110, 111] pharmacy refill data in one study,[111] pill counts in one study,[112] and self-reported measures in two studies.[111, 113] Self-reported measures in one study included a Morisky scale and a general adherence score;[113] in another study, self-reported measures included an adherence questionnaire.[111] One of the four studies used multiple measures of adherence including MEMS caps, pharmacy refill data, and self-reported adherence.[111]

All four studies reported additional outcomes. One study reported mortality outcomes.[113] Three studies reported quality-of-life measures, including the Minnesota Living with Heart Failure (MLHF) and the SF-36 questionnaires in one study,[110] a Chronic Heart Failure questionnaire in another study,[111] and the Kansas City Cardiomyopathy questionnaire in the third study.[113] Two studies reported patient satisfaction outcomes; one used a self-reported validated questionnaire,[111] another used a modified Art of Medicine patient satisfaction questionnaire.[113] All-cause Emergency Department (ED) visits were reported in two studies,[111, 113] and all-cause hospitalizations were reported in three studies.[111-113] Among the three studies reporting all-cause hospitalizations, two studies reported both the number of patients hospitalized and total number of hospitalizations.[112, 113] One of the three studies reporting all-cause hospitalizations additionally reported total hospitalization days.[112] One study reported multiple composite measures, including combined all-cause ED visits and hospitalizations, combined cardiovascular-related ED visits and hospitalizations, and combined heart failure-related ED visits and hospitalizations.[111] One study reported both the number of patients that were seen in a heart failure clinic and the total visits to the heart failure clinic in each group. Only one study evaluated costs (inpatient, outpatient, and combined).[111]

Timing

The duration of interventions varied among the four studies: the shortest intervention lasted 1 month[112] and the longest lasted 12 months.[113] One study reported adherence outcomes both during and at the conclusion of the intervention.[113] The other three studies reported adherence outcomes at the conclusion of the intervention.[110-112] Two studies additionally reported adherence outcomes after interventions had concluded: one at 2 weeks following an intervention,[110] and one in 3 months following completion of an intervention.[111] Health care utilization measures of ED visits and hospitalizations were reported for a 12-month period in one study that was a 9-month intervention followed by an additional 3-month postintervention evaluation period.[111] In another study with a 30-day intervention, health care utilization measures of ED visits and hospitalizations were reported for 90 days.[112] The period of evaluation was unclear in the other study that reported ED visits and hospitalizations.[113] The study that reported cost and patient satisfaction reported these measures for 12 months; this study reported quality of life at 6 and 12 months.[111]

Setting

Settings varied among the four studies. One study focused on a population recruited from an urban home health agency and ambulatory care clinic.[110] Three studies focused on populations cared for in a university-affiliated system: one recruited patients from an academic primary care practice and an urban university-affiliated hospital,[111] the second recruited patients admitted to a university teaching hospital with a heart failure exacerbation,[112] and the third study recruited patients from a heart failure specialty clinic.[113] Interventions also took place in variable settings: patient homes in one study,[110] a pharmacy in another study,[111] both inpatient and outpatient settings in one study,[112] and within a heart failure specialty clinic in the final study.[113]

Applicability

Notable limitations to applicability included the following: a low participation rate (10 percent) among those eligible in one study;[110] significant differences between participants versus those who declined to participate (lower income, less education, less access to home computers, and other differences among decliners) in another study;[113] and the high complexity of one intervention that involved at least four disciplines of health professionals and both inpatient and outpatient components.[112]

Key Points

- Across all four studies, we found evidence suggestive of improved medication adherence.

Video and Telephone Reminder Intervention

- Medication adherence: In a single, small study with limited followup, we found evidence of improved medication adherence (low strength of evidence).
- Quality of life: This study reported Minnesota Living with Heart Failure scores, which were not different between intervention and control groups, but did improve significantly in all groups from baseline to followup. This study also reported SF-36 scores, which did not significantly differ between groups or improve from baseline to followup. Because of the lack of precision, we were unable to make a conclusion

about the true effect of the intervention on quality-of-life outcomes and graded the strength of evidence outcomes as insufficient.

Pharmacist-led Multicomponent Intervention

- Medication adherence: This study demonstrated improved medication adherence in the intervention group compared with controls with objective measures including MEMS caps and pharmacy refill data, but did not find improved adherence with a self-reported measure during the 9-month intervention (low strength of evidence for the 9-month duration of the intervention).
- In addition, this study did not show evidence that the intervention effect was sustained in the 3 months following the intervention, with loss of all significant differences in adherence between groups.
- Quality of life: This study demonstrated no significant difference in disease-specific quality of life between intervention and control groups at two time points due to imprecise outcomes (insufficient evidence).
- Patient satisfaction: This study demonstrated improved patient satisfaction outcomes in the intervention group compared with the control group (low strength of evidence).
- Healthcare utilization: This study demonstrated evidence of benefit for all-cause ED visits and combined all-cause ED and hospitalization (low strength of evidence); however, no evidence of benefit was demonstrated for all other healthcare utilization measures, including all-cause hospitalizations, combined cardiovascular ED visits and hospitalizations, and combined heart failure-related ED visits and hospitalizations due to imprecise outcomes (insufficient evidence).
- This study demonstrated no evidence of benefit for inpatient costs, outpatient costs, and combined inpatient and outpatient costs, due to imprecision (insufficient evidence).

Case Management (Multisetting, Multidisciplinary Intervention)

- Medication adherence: This single study of relatively small size demonstrated evidence of short-term adherence benefit; adherence outcomes spanned only 30 days (low strength of evidence).
- Healthcare utilization: This study demonstrated imprecise outcomes for readmission (insufficient evidence).

Access to Medical Records

- Medication adherence: We found the evidence for this study insufficient to rate strength of evidence due to imprecise and variable adherence outcomes (insufficient evidence).
- Mortality, quality of life, patient satisfaction, all-cause hospitalizations, ED visits, and heart failure-related visits: This study demonstrated imprecise outcomes for all other outcomes (insufficient evidence).

Detailed Synthesis for Heart Failure

All four of the randomized controlled trials in populations with heart failure showed statistically significant improvement in at least one measure of medication adherence in the intervention group compared with the control group (Table 30).[110-113] We evaluated other

outcomes for all four studies because all reported some degree of improvement in medication adherence (Table 31 through Table 35). The results for this body of evidence, although suggestive of improvement in adherence during interventions, need to be evaluated in the context of heterogeneous interventions and measures. We found no evidence of sustained adherence improvements following the end of the interventions: no study evaluated outcomes beyond the 3-month mark after the intervention ended. The mixed results related to health care utilization should also be interpreted in the context of heterogeneous interventions and outcomes (Table 34). Because the components of the four interventions were so heterogeneous, they were not grouped to evaluate strength of evidence. Strength of evidence was completed for all studies, and tables were created only for studies that had more than insufficient evidence for any outcome (Table 35 through Table 37).[110-112]

Detailed Synthesis for Heart Failure for Video and Telephone Reminder Intervention

Medication Adherence

In a study of video and telephone reminder calls, the two intervention groups showed higher rates of medication adherence (84 percent and 74 percent)—MEMS caps measures—than the control group (57 percent) 2 weeks following an intervention (Table 30).[110] However, control group decline in adherence from baseline (81 percent) to followup (57 percent) comprised much of the difference identified between intervention and control groups. We found low strength of evidence of improved adherence from this study (Table 36).

Other Outcomes

This study of video and telephone reminder calls reported scores from the Minnesota Living with Heart Failure (MLHF) questionnaire, which did not differ between groups at 10 weeks, but improved significantly ($p<0.001$) in all groups from baseline to 10 weeks (Table 33).[110] This study also reported scores from the SF-36 questionnaire, which did not differ between groups at 10 weeks, nor did scores change significantly in any group from baseline to followup.[110] Because of the lack of precision, we were unable to make a conclusion about the true effect of the intervention on quality-of-life outcomes and graded strength of evidence as insufficient (Table 36).

Detailed Synthesis for Heart Failure for Pharmacist-led Multicomponent Intervention

Medication Adherence

In a pharmacist intervention, MEMS caps adherence measures of “taking adherence” (percent of prescribed medication doses taken based on physician's prescription) and “scheduling adherence” (taking medications within a similar time frame each day) were significantly better in the intervention group (78.8 percent taking and 53.1 percent scheduling adherence) compared with the control group (67.9 percent taking and 47.2 percent scheduling adherence) at the end of a 9-month intervention (Table 30).[111] However, when the same outcomes were measured 3 months following completion of the intervention, significant differences between the intervention and control groups were lost. This pharmacist study also measured adherence with a medication possession ratio (MPR) from pharmacy refill data and found significantly higher

MPR in the intervention group (109.4 percent) than in the control group (105.2 percent) over 1 year; the study included 9 months of intervention and 3 months postintervention.[111] Of interest, this study found no difference between self-reported adherence between intervention and control groups at 9 months.[111] We found low strength of evidence for improved adherence during the 9-month intervention (Table 37).

Other Outcomes

This study of a pharmacist intervention reported questionnaire-obtained Heart Failure quality of life data; changes from baseline to 6 months and from baseline to 12 months did not differ significantly between groups (Table 32).[111] This study also reported patient satisfaction with pharmacy services and found a significant improvement from baseline to 12 months in the intervention group compared with the control group (Table 33).[111] This study found significantly fewer all-cause ED visits and combined all-cause ED visits and hospitalizations over 12 months in the intervention group compared with the control group (Table 34).[111] However, this study did not identify significant differences between the intervention and control groups for all-cause hospitalizations, combined cardiovascular-related ED visits and hospitalizations, or combined heart failure-related ED visits and hospitalizations over 12 months.[111] Finally, this study evaluated costs for outpatient health care costs, inpatient healthcare costs, and the sum of inpatient and outpatient costs, none of which differed significantly between intervention and control groups for the year (Table 35).[111] In sum, we found low strength of evidence of benefit for patient satisfaction and for health care utilization outcomes of all-cause ED visits and combined all-cause ED visits and hospitalizations (Table 37). Because of the lack of precision, we were unable to make a conclusion about the true effect of the intervention on all other outcomes and graded the evidence as insufficient for all other outcomes.

Detailed Synthesis for Heart Failure for Case Management (Multisetting, Multidisciplinary Intervention)

Medication Adherence

In the study of a multidisciplinary, multisetting intervention, pill count measures were used to derive multiple measures of adherence including the percentage of medications taken correctly, both averaged by medication and pooled overall, and the proportion of participants with 80 percent and great adherence and 90 percent and greater adherence.[112] All measures improved significantly in the intervention group compared with the control group at 30-day followup.[112] We found low strength of evidence of improved adherence from this study (Table 38).

Other Outcomes

This study of a multidisciplinary, multisetting intervention did not find significant differences between groups in the number of patients with all-cause hospital admissions, total all-cause hospital admissions, or days of all-cause hospital admissions.[112] Evidence was judged insufficient to grade strength of evidence related to these outcomes due to imprecision (Table 38).

Detailed Synthesis for Heart Failure for Access to Medical Records

Medication Adherence

In the study in which access to an online medical record was provided to the intervention group, self-reported Morisky scores and General Adherence Scores were collected at 6 and 12 months to assess adherence.[113] While no difference was found in Morisky scores between intervention and control groups at 6 or 12 months, an improvement in the General Adherence Score was found in the intervention group compared with the control group at 12 months, but not at 6 months. Because of indirectness related to the General Adherence Scores and imprecise adherence outcomes related to the Morisky scores (Table 38), we could not judge the true effect of the intervention and rated the evidence as insufficient.

Other Outcomes

This study reported mortality outcomes (Table 31), which did not differ between intervention and control groups.[113] This study also reported quality-of-life outcomes in specific domains from the Kansas City Cardiomyopathy questionnaire (Table 32). Symptom stability was the only quality-of-life domain that appeared to differ between groups; however, when adjusted for multiple comparisons, this difference lost statistical significance. This study also reported patient satisfaction outcomes, which, when adjusted for multiple comparisons, did not significantly differ between groups (Table 33). Of interest, in this study, intervention patients had significantly more all-cause ED visits in the intervention group than the control group (20 versus 8 visits, p=0.03); however, the number of patients with ED visits did not differ significantly between groups (Table 34).[113] This study did not identify significant differences between the intervention and control groups for all-cause hospitalizations or for heart failure practice visits.[113] Because of imprecise outcomes, we could not judge the true effect of the intervention and rated the evidence as insufficient (Table 38).

Table 29. Heart failure: study characteristics

Author, Year N at Randomization	Population Setting	Intervention and Comparator
Fulmer et al., 1999[110] N=60	Adults ≥65 years old with a diagnosis of heart failure; use of an ACE inhibitor, calcium channel blocker, or beta-blocker Urban home health care agency and ambulatory care clinic	G1: For 6 weeks, participants received video reminder calls to take their medications daily (Monday through Friday). The call consisted of a brief greeting and a question about whether the previous day's medication had been taken, and additional time to answer patients' questions. G2: This group received the same intervention as G1, but via regular phone call with no video component. G3: Received no reminder calls.
Murray et al., 2007[111] N=314	Adults ≥50 years old with heart failure Pharmacy	G1: Pharmacist-led intervention providing verbal instructions, literacy-sensitive written materials and labeling of medications with icons to promote medication adherence. G2: No contact with intervention pharmacist other than initial medication history.
Rich et al., 1996[112] N=156	Adults ≥70 years old hospitalized with heart failure University teaching hospital	G1: While inpatient, received teaching about heart failure, daily visits by study nurse to emphasize medication compliance, visits by dietician and social services, medication review by geriatric cardiologist prior to discharge; following discharge, homecare department visits and regular telephone contact by study nurse. G2: Conventional care by regular physician, standard hospital services including teaching and medication instructions.
Ross et al., 2004[113] N=107	Adults ≥18 years old with heart failure Heart failure specialty clinic	G1: Provided with access to online medical record, online access to an educational guide for heart failure, and access to a messaging system to communicate with nursing staff. G2: Received standard care without access to online medical record or messaging system. Received same heart failure educational guide as printed materials.

Abbreviations: ACE, angiotensin-converting enzyme; G, group; N, number.

Table 30. Heart failure: medication adherence

Study N Analyzed for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
Fulmer et al., 1999[110] G1: 17 G2: 15 G3: 18	Compliance rates monitored during a 2-week pre-intervention phase (baseline), 6-week intervention phase (time 2), and 2-week postintervention phase (time 3) MEMS/Nonself-report	Average compliance rates baseline: G1: 82% G2: 76% G3: 81% Time 3: G1: 84% G2: 74% G3: 57% (significantly decreased from baseline at p<0.04) 95% CI, NR p: There was a statistically significant time effect during the course of the study from baseline to postintervention (F=4.08, p<0.05) in which G1 and G2 showed enhanced compliance relative to G3. However, there was no significant difference between compliance in G1 and G2.
Murray et al., 2007[111] G1: 122 G2: 192	"Taking Adherence": Percentage of prescribed medication doses taken based on physician's prescription (during 9-month intervention): MEMS/Nonself-report	Proportion (95% CI) G1: 78.8% (74.9 to 82.7) G2: 67.9% (63.8 to 72.1) Difference: 10.9% (5.0 to 16.7) p: Not Reported (NR)
G1: 122 G2: 192	"Taking Adherence": Percentage of prescribed medication doses taken based on physician's prescription (in 3 months following intervention): MEMS/Nonself-report	Proportion (95% CI) G1: 70.6% (64.9 to 76.2) G2: 66.7% (62.3 to 70.9) Difference: 3.9% (-2.8 to 10.7) p: NR
G1: 122 G2: 192	"Scheduling Adherence": Measure of adherence to timing, lower with day-to-day deviation in the timing of medication administration (during 9-month intervention): MEMS/Nonself-report	Proportion (95% CI) G1: 53.1% (49.1 to 57.1) G2: 47.2% (43.4- to 0.9) Difference: 5.9% (0.4 to 11.5) p: NR
G1: 122 G2: 192	"Scheduling Adherence": Measure of adherence to timing, lower with day-to-day deviation in the timing of medication administration (in 3 months following intervention): MEMS/Nonself-report	Proportion (95% CI) G1: 48.9% (43.7 to 54.1) G2: 48.6% (44.7 to 52.6) Difference: 0.3 (-5.9 to 6.5) p: NR
G1: NR G2: NR	Medication possession ratio over 1 year (meds received relative to meds prescribed) Pharmacy refill data/Nonself-report	G1: 109.4% G2: 105.2% Difference: 4.2% 95% CI, NR p=0.007
G1: NR G2: NR	Self-reported adherence from questionnaire at baseline and 9 months Self-report	G1: 1.0 G2: 0.8 95% CI, NR p=0.48
Rich et al., 1996[112] G1: 80 G2: 76	Percentage of pills taken correctly for each current medication, then averaged at 30 days after discharge Pill count/Nonself-report	G1: 87.9% (SD 12.0) G2: 81.1% (SD 17.2) 95% CI, NR p=0.003

Table 30. Heart failure: medication adherence (continued)

Study N Analyzed for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
G1: 80 G2: 76	Proportion with ≥80% medication compliance by above method (averaged) Pill count/Nonself-report	G1: 85.0% G2: 69.7% 95% CI, NR p=0.036
G1: 80 G2: 76	Percentage of pills taken correctly for all current medications, pooled at 30 days after discharge Pill count/Nonself-report	G1: 87.5% (SD 12.6) G2: 80.9% (SD 16.7) 95% CI, NR p=0.003
G1: 80 G2: 76	Proportion with ≥80% medication compliance by above method (pooled) Pill count/Nonself-report	G1: 82.5% G2: 66.2% 95% CI, NR p=0.033
G1: 80 G2: 76	Proportion with ≥90% medication compliance, unclear which method used (averaged or pooled) Pill count/Nonself-report	G1: 56.3% G2: 34.2% 95% CI, NR p=0.032
Ross et al., 2004[113] G1: NR G2: NR	Medication Adherence Score 4-point Morisky score (higher score indicating better adherence)/Self-report	6 months: G1: 3.5 mean G2: 3.4 mean Difference: 0.1 (95% CI, -0.2 to 0.4) p: NR 12 months: G1: 3.6 mean G2: 3.4 mean Difference: 0.2 (95% CI, -0.1 to 0.6) p=0.15
G1: NR G2: NR	General Adherence Score from Medical Outcomes Study 100-point scale (a higher score indicates better adherence)/Self-report	6 months: G1: 81 mean G2: 78 mean Difference: 2.3 (95% CI, -3.7 to8.3) p: NR 12 months: G1: 85 mean G2: 78 mean Difference: 6.4 (95% CI, 1.8 to10.9) p=0.01 (0.02 adjusted for multiple comparisons)

Abbreviations: CI, confidence interval; G, group; MEMS, Medication Event Monitoring System; N, number; NR, not reported; SD, standard deviation.

Table 31. Heart failure: mortality

Author, Year N in Each Group	Outcome	Results
Ross et al., 2004[113] G1: NR G2: NR	Deaths (%)	G1: 6 (11%) G2: 6 (11%) 95% CI, NR p=1.00

Abbreviations: CI, confidence interval; G, group; NR, not reported.

Table 32. Heart failure: quality of life

Author, Year N in Each Group	Outcome	Results
Fulmer et al., 1999[110] G1: 15 G2: 13 G3: 14	MLHF questionnaire score 21-item scale, each item scored 0 to 5 (lower score indicates lower impact of heart failure treatment on quality of life) /Self-report	Baseline mean score (SD) G1: 43.1 (20.8) G2: 54.4 (21.1) G3: 46.6 (27.7) 95% CI, NR p: NR 10-week mean score (SD) G1: 36.7 (19.9) G2: 32.9 (25.2) G3: 32.9 (22.9) 95% CI, NR p: NR Per text, all groups had an improvement in MLHF scores from baseline to followup (p<0.001) that did not differ between groups.
G1: 15 G2: 13 G3: 14	SF-36 score 100-point scale (higher score indicates more favorable state of health)/Self-report	Baseline mean score (SD) G1: 86.1 (17.0) G2: 81.0 (15.2) G3: 87.3 (24.3) 95% CI, NR p: NR 10-week mean score (SD) G1: 85.9 (18.9) G2: 90.1 (20.6) G3: 91.7 (22.7) 95% CI, NR p: NR Per text “there was no significant change in the SF-36 scores for the sample… Group membership did not make a difference…”
Murray et al., 2007[111] G1: NR G2: NR	Improved Chronic Heart Failure Questionnaire Average scores (range 1-7) from 4 dimensions (higher scores indicate better function)/Self-report	Change from baseline at 6 months: G1: 0.28 G2: 0.21 95% CI, NR p=0.52 Change from baseline at 12 months: G1: 0.39 G2: 0.24 95% CI, NR p=0.21
Ross et al., 2004[113] G1: NR G2: NR	Results from KCCQ domains scored 1 to 100 (higher scores indicate higher quality of life) Self-efficacy	Baseline average for both groups: 85 6 months: G1: 88 G2: 84 Difference: 4 95% CI: -3, 9 p: NR 12 months: G1: 91 G2: 85 Difference: 6 95% CI: -1, 11 p=0.08

Table 32. Heart failure: quality of life (continued)

Author, Year N in Each Group	Outcome	Results
	Symptom stability	Baseline average for both groups: 49 6 months: G1: 45 G2: 49 Difference: -4 95% CI: -15, 6 p: NR 12 months: G1: 63 G2: 46 Difference: 17 95% CI: 4, 29 p<0.01; p=0.06 when adjusted for multiple comparisons
	Symptoms	Baseline average for both groups: 63 6 months: G1: 61 G2: 65 Difference: -4 95% CI: -11, 3 p: NR 12 months: G1: 64 G2: 65 Difference: 0 95% CI: -8, 8 p=0.96
	Quality of life	Baseline average for both groups: 56 6 months: G1: 64 G2: 59 Difference: 5 95% CI: -5, 13 p: NR 12 months: G1: 64 G2: 62 Difference: 2 95% CI: -7, 11 p=0.63
	Functional status	Baseline average for both groups: 66 6 months: G1: 63 G2: 69 Difference: -6 95% CI: -12, 0 p: NR 12 months: G1: 67 G2: 70 Difference: -3 95% CI: -11, 3 p=0.31

Table 32. Heart failure: quality of life (continued)

Author, Year N in Each Group	Outcome	Results
	Clinical summary	Baseline average for both groups: 64 6 months: G1: 62 G2: 66 Difference: -4 95% CI: -10, 2 p: NR 12 months: G1: 69 G2: 66 Difference: -3 95% CI: -10, 4 p=0.38
	Physical limitations	Baseline average for both groups: 66 6 months: G1: 63 G2: 70 Difference: -7 95% CI: -13, -1 p: NR 12 months: G1: 69 G2: 73 Difference: -4 95% CI: -12, 3 p=0.26

Abbreviations: CI, confidence interval; G, group; ; KCCQ, Kansas City Cardiomyopathy Questionnaire; MLHF, Minnesota Living with Heart Failure; NR, not reported, SD, standard deviation; SF-36, Short Form (36) Health Survey.

Table 33. Heart failure: patient satisfaction

Author, Year N in Each Group	Outcome	Results
Murray et al., 2007[111] G1: NR G2: NR	Improvement in patient satisfaction with pharmacy services from baseline to 12 months 12-item validated instrument (unclear directionality)/Self-report	G1: 1.0 G2: 0.7 95% CI, NR p=0.022
Ross et al., 2004[113] G1: NR G2: NR	Modified Art of Medicine questionnaire; patient satisfaction scored 1 to 5 (higher score indicates higher satisfaction)/Self-report "Overall, how well do the heart doctors understand your problems?"	Baseline average for both groups: 4.5 6 months: G1: 4.4 G2: 4.4 Difference: 0 95% CI: -0.3, 0.2 p: NR 12 months: G1: 4.6 G2: 4.2 Difference: 0.4 95% CI: 0.1, 0.6 p=0.02; 0.13 when adjusted for multiple comparisons
	"Overall, how well do the heart doctors explain to you what they are doing and why?"	Baseline average for both groups: 4.2 6 months: G1: 4.5 G2: 4.1 Difference: 0.4 95% CI: 0.1, 0.7 p: NR 12 months: G1: 4.5 G2: 4.1 Difference: 0.4 95% CI: 0.1, 0.7 p=0.02, 0.13 when adjusted for multiple comparisons
	"Overall, how well do the heart doctors speak to you using words that are easy for you to understand?"	Baseline average for both groups: 4.2 6 months: G1: 4.2 G2: 4.3 Difference: -0.1 95% CI: -0.4, 0.1 p: NR 12 months: G1: 4.1 G2: 4.3 Difference: -0.2 95% CI: -0.5, 0.1 p=0.15
	"Overall, how well do the heart doctors listen to your concerns and questions?"	Baseline average for both groups: 6 months: 4.5 G1: 4.6 G2: 4.3 Difference: 0.3 95% CI: 0.02, 0.5 p: NR 12 months: G1: 4.5 G2: 4.3 Difference: 0.2 95% CI: -0.1, 0.5 p=0.26

Table 33. Heart failure: patient satisfaction (continued)

Author, Year N in Each Group	Outcome	Results
	"Overall, how much confidence do you have in the ability or competence of the heart doctors?"	Baseline average for both groups: 4.5 6 months: G1: 4.6 G2: 4.4 Difference: 0.2 95% CI: -0.1, 0.4 p: NR 12 months: G1: 4.5 G2: 4.5 Difference: 0 95% CI: -0.2, 0.3 p=0.80
	"Overall, how satisfied are you with the service that you received from the heart doctors?"	Baseline average for both groups: 4.5 6 months: G1: 4.5 G2: 4.5 Difference: 0 95% CI: -0.2, 0.3 p: NR 12 months: G1: 4.6 G2: 4.4 Difference: 0.2 95% CI: -0.2, 0.5 p=0.07; 0.30 when adjusted for multiple comparisons

Abbreviations: CI, confidence interval; G, group; NR, not reported.

Table 34. Heart failure: healthcare utilization including emergency department visits, hospitalizations, and clinic visits

Author, Year N in Each Group	Outcome	Results
Murray et al., 2007[111] G1: 122 G2: 192	All-cause ED visits over 12 months	Mean (SD) G1: 2.16 (3.31), 1 median G2: 2.68 (4.87), 1 median IRR: 0.82 95% CI, 0.70, 0.95 p: NR
G1: 122 G2: 192	All-cause hospitalizations over 12 months	Mean (SD) G1: 0.78 (1.66), 0 median G2: 0.97 (1.78), 0 median IRR: 0.81 95% CI, 0.64, 1.04 p: NR
G1: 122 G2: 192	Combined all-cause ED visits and hospitalizations over 12 months	Mean (SD) G1: 2.94 (4.69), 1 median G2: 3.65 (6.26), 1.5 median IRR: 0.82 95% CI, 0.72, 0.93 p: NR
G1: 122 G2: 192	Combined cardiovascular-related ED visits and hospitalizations over 12 months	Mean (SD) G1: 0.61 (1.72) G2: 0.67 (1.95) IRR 0.96 95% CI, 0.48 to 1.91 p: NR

Table 34. Heart failure: healthcare utilization including emergency department visits, hospitalizations, and clinic visits (continued)

Author, Year N in Each Group	Outcome	Results
G1: 122 G2: 192	Combined heart failure-related ED visits and hospitalizations over 12 months	Mean (SD) G1: 0.40 (1.47) G2: 0.44 (1.79) IRR 1.00 (95% CI, 0.36 to 2.77) p: NR
Rich et al., 1996[112] G1: 80 G2: 76	Number of patients with all-cause readmissions at 90 days following discharge	G1: 22.5% G2: 28.9% 95% CI, NR p: NR, not significant
G1: 80 G2: 76	Number of all-cause readmissions at 90 days following discharge	G1: 22 G2: 31 95% CI, NR p: NR, not significant
G1: 80 G2: 76	Days of all-cause hospitalization from readmissions	G1: 188 G2: 258 95% CI, NR p: NR, not significant
Ross et al., 2004[113] G1: NR G2: NR	Number of patients with all-cause hospitalizations (%)	G1: 11 (20%) G2: 12 (23%) 95% CI, NR p=0.81
G1: NR G2: NR	Number of all-cause hospitalizations	G1: 22 G2: 21 95% CI, NR p=1.00
G1: NR G2: NR	Number of patients with all-cause ED visits (%)	G1: 11 (20%) G2: 7 (13%) 95% CI, NR p=0.44
G1: NR G2: NR	Number of all-cause ED visits	G1: 20 G2: 8 95% CI, NR p=0.03
G1: NR G2: NR	Number of patients with heart failure practice visits (%)	G1: 50 (93%) G2: 49 (92%) 95% CI, NR p=1.00
G1: NR G2: NR	Number of heart failure practice visits	G1: 324 G2: 325 95% CI, NR p=0.66

Abbreviation: CI, confidence interval; ED, emergency department; G, group; IRR, incidence rate ratio; relative risk; NR, not reported; SD, standard deviation.

Table 35. Heart failure: cost

Author, Year N in Each Group	Outcome	Results
Murray et al., 2007[111] G1: 122 G2: 192	Annual outpatient health care costs	Mean (SD) G1: $5,483 (6,434) G2: $6,373 (6,501) Difference: -866 95% CI, -2,289 to 660 p: NR
G1: 122 G2: 192	Annual inpatient health care costs	Mean (SD) G1: $5,550 (13,847) G2: $7,827 (20,413) Difference: -2277 95% CI, -6,329 to 1,225 p: NR
G1: 122 G2: 192	Annual total health care costs (inpatient + outpatient)	Mean (SD) G1: $11,034 (17,211) G2: $14,199 (23,672) Difference: -3165 95% CI, -7,800 to 1,138 p: NR

Abbreviations: CI, confidence interval; G, group; NR, not reported; SD, standard deviation.

Table 36. Heart failure: strength of evidence for reminders delivered by video and telephone

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Heart Failure: Video and telephone reminders	1; 60 (50)	Medication Adherence	RCT Medium	Unknown	Indirect	Precise	Difference of 17-27 percentage points in adherence Low
	0	Biomarkers	NA	NA	NA	NA	Insufficient
	0	Mortality	NA	NA	NA	NA	Insufficient
	0	Morbidity	NA	NA	NA	NA	Insufficient
	1; 60 (42)	Quality of life	RCT Medium	Unknown	Direct	Imprecise	Insufficient
	0	Patient satisfaction	NA	NA	NA	NA	Insufficient
	0	Health care Utilization	NA	NA	NA	NA	Insufficient
	0	Quality of care	NA	NA	NA	NA	Insufficient

Abbreviations. NA, not applicable; RCT, randomized controlled trial

Table 37. Heart failure: strength of evidence for pharmacist-led multicomponent intervention

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Heart Failure Pharmacist-led intervention	1; 314 (314 for MEMS caps, NR for MPR or self-report)	Medication Adherence	RCT Medium	Unknown	Direct	Precise	Difference in percentage points for taking medication (MEMS) at 9 months: 10.9 Difference in percentage points for adherence to timing (MEMS) at 9 months: 5.9 Difference in percentage points in MPR over 12 months: 4.2 No significant difference for self-report Low
	0	Mortality	NA	NA	NA	NA	Insufficient
	0	Morbidity	NA	NA	NA	NA	Insufficient
	1; 314 (314)	Quality of life	RCT Medium	Unknown	Direct	Imprecise	Insufficient
	1; 314 (314)	Patient satisfaction	RCT Medium	Unknown	Direct	Precise	Difference of 0.3 on validated questionnaire Low
	1; 314 (314)	Health care utilization: All-cause ED visits, hosp, and Combined ED visits & hosp	RCT Medium	Unknown	Direct	Precise for all-cause ED visits and all-cause ED+hosp; Imprecise for all-cause hosp	Difference of 0.52 all-cause ED visits and 0.69 all-cause ED+hosp Low All-cause hosp Insufficient
	1; 314 (314)	Health care utilization: CV-related and HF related events	RCT Medium	Unknown	Direct	Imprecise	Insufficient
	1; 314 (314)	Costs	RCT Medium	Unknown	Direct	Imprecise	Insufficient
	0	Quality of care	NA	NA	NA	NA	Insufficient

Abbreviations: CV, cardiovascular; diff, difference; ED, emergency department; G, group; HF, heart failure; Hosp, hospitalization; MEMS, medication event monitoring system; MPR, medication possession ratio; NA, not applicable; NR, not reported; RCT, randomized controlled trial.

Table 38. Heart failure: strength of evidence for case management (multisetting, multidisciplinary intervention)

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Heart Failure Multi disciplinary, multisetting intervention	1; 156; (156)	Medication Adherence	RCT Medium	Unknown	Direct	Precise	Difference in percentage points in med adherence: 6.6-6.8 (range) Difference in percentage points in proportion with ≥80% adherence: 15.7 to 16.3 Low
	0	Mortality	NA	NA	NA	NA	Insufficient
	0	Biomarkers	NA	NA	NA	NA	Insufficient
	0	Morbidity	NA	NA	NA	NA	Insufficient
	0	Quality of life	NA	NA	NA	NA	Insufficient
	0	Patient satisfaction	NA	NA	NA	NA	Insufficient
	0	Health care Utilization: All-cause hospital readmission	RCT Medium	Unknown	Direct	Imprecise	No significant difference in all-cause readmission Insufficient
	0	Quality of care	NA	NA	NA	NA	Insufficient

Abbreviations: G, group; med, medication; RCT, randomized controlled trial.

Key Question 1. Myocardial Infarction Medication Adherence Interventions

Description of Included Study

Overview

We found one study, with medium risk of bias, that evaluated an intervention to improve medication adherence among patients with a recent myocardial infarction.[114] Table 39 presents an overview of the intervention. Table 40 present results for medication adherence and is followed by a strength of evidence table (Table 41).

Population

This study was conducted in adults ages 18 and older with a mean participant age of between 64 and 65 years old. Women comprised between 31–34 percent of the study population.

Intervention

The intervention in this study was targeted at both patients and providers. The intervention consisted of two mailed communications approximately 2 months apart that primarily stressed the importance of using beta blockers following myocardial infarctions (Table 39). Primary care clinicians caring for patients randomized to the intervention arm also received a letter that alerted them that their patients would be receiving the mailed materials and encouraged their support of the initiative. In the control arm, neither patients nor their primary care clinicians received these communications.

Outcome and Timing

This study did not report on initiation of medication. Medication adherence outcomes were determined from pharmacy refill data and included the absolute increase in proportion of days covered per month from baseline to followup and the likelihood of having 80 percent or more of medications across the entire 9-month period. Medication persistence outcomes were also determined from pharmacy refill data and included the proportion with gaps of 1, 2, 3, and 4 months in length between filling beta-blocker prescriptions. This study did not report additional morbidity, mortality, or other outcomes beyond adherence and persistence.

The intervention lasted approximately 1 month, which spanned the time between two mailings to patients. This study measured adherence and persistence across 9 months.

Setting

This study was based in primary care clinics.

Applicability

This limited evidence base curtails our ability to make conclusions about applicability.

Key Points

- In one study of an intervention that targeted patients and providers with mailed interventions following a myocardial infarction, we found evidence suggestive of improved medication adherence (low strength of evidence).
- Our strength of evidence grade is based on having a single study with a small, marginally statistically significant relative risk of improved adherence and a small absolute improvement in adherence in the intervention arm compared with the control arm of unclear clinical significance.
- The study reported persistence data and found no difference between intervention and control groups (insufficient).

Detailed Synthesis for Interventions Directed at Patients and Providers Through Mailed Communications for Myocardial Infarction

The study we identified in patients with recent myocardial infarction showed statistically significant improvement in medication adherence outcomes but not in persistence outcomes in the intervention group compared with the control group (Table 40).[114] The study found statistically significant improvement in adherence in the intervention group with a 4.3 percent mean absolute increase in proportion of days covered per month from baseline to 9 months in the intervention group compared with the control group (p=0.04). The study also noted improved adherence in the likelihood of having 80 percent or more of medications across the entire 9-month period in the intervention group (64.8 percent) compared with the control group (58.5 percent). However, the study found no significant differences between groups in the proportion of patients with gaps of 1, 2, 3, or 4 months between beta-blocker prescriptions.

We graded strength of evidence for this intervention. This study showed low strength of evidence for improved medication adherence and insufficient evidence for medication persistence (Table 41).

Table 39. Medication adherence interventions for other cardiovascular diseases and CVD risk factors: study characteristics

Author, Year N at Randomization	Population Setting	Intervention and Comparator
Smith et al., 2008[114] N=907	Adults ≥18 years old with a myocardial infarction Primary care clinics	G1: 2 mailed communications to patients encouraging beta blocker adherence; mailed communication to primary care providers G2: usual care (no mailings)

Abbreviations: G, group; N, number.

Table 40. Medication adherence interventions for other cardiovascular diseases and multiple CVD risk factors: medication adherence

Study N Analyzed for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
Smith et al., 2008[114] G1: 426 G2: 410	Absolute increase in proportion of days covered per month for the entire 9-month follow-up period: Pharmacy refill data	G1: 4.3% mean absolute increase in days covered per month compared with G2 95% CI, NR p=0.04
G1: 426 G2: 410	Likelihood of having at least 80% proportion of days covered across 9 months of followup: Pharmacy refill data	G1: 64.8% G2: 58.5% Relative risk: 1.17 95% CI, 1.02 to 1.29
G1: NR G2: NR	Among patients in possession of a beta-blocker prescription at the time of the intervention: proportion of group with a gap in refilling beta-blocker Pharmacy refill data	1-month gap: G1:104 (23%) G2: 110 (25%) HR 0.85 (0.65 to 1.12) Adjusted HR 0.89 (0.67 to 1.19) 2-month gap G1:63 (14%) G2: 67 (15%) HR 0.86 (0.61 to 1.22) Adjusted HR 0.95 (0.67 to 1.33) 3-month gap G1: 43 (9%) G2: 51 (12%) HR 0.77 (0.51 to 1.16) Adjusted HR 0.87 (0.60 to 1.26) 4-month gap G1: 30 (7%) G2: 37 (9%) HR 0.74 (0.46 to 1.20) Adjusted HR 0.85 (0.54 to 1.35)

Abbreviations: CI, confidence interval; G, group; HR, hazard ratio; NR, not reported

Table 41. Medication adherence interventions for myocardial infarction: strength of evidence for mailed intervention targeting patients and providers

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Myocardial Infarction: Mailed intervention targeting patients and providers	1; 907(836)	Medication Adherence	RCT Medium	Unknown	Direct	Precise	Difference in percentage points in absolute mean increase in adherence over 9 months: 4.3 Differences in percentage points in proportion of ≥80% adherence: 6% Low
	1; 907(NR)	Medication Persistence	RCT Medium	Unknown	Direct	Imprecise	Insufficient
	0	Mortality	NA	NA	NA	NA	Insufficient
	0	Morbidity symptoms	NA	NA	NA	NA	Insufficient
	0	Quality of life	NA	NA	NA	NA	Insufficient
	0	Patient satisfaction	NA	NA	NA	NA	Insufficient
	0	Healthcare utilization	NA	NA	NA	NA	Insufficient
	0	Quality of care	NA	NA	NA	NA	Insufficient

Abbreviations: NA, not applicable; NR, not reported; NS, not significant; RCT, randomized controlled trial.

Key Question 1. Reactive Airway Diseases: Medication Adherence Interventions (Asthma or Chronic Obstructive Pulmonary Disease)

Description of Included Studies

Overview

We found eight studies that attempt to improve medication adherence among patients with asthma[115-122] or asthma or chronic obstructive pulmonary disease (COPD) (Table 42). We rated three studies as having low risk of bias[116, 120, 121] and five as having medium risk of bias.[115, 117-119, 122] Table 42 presents an overview of the interventions. Table 43 through Table 47 present results for medication adherence and other outcomes for all studies, followed by strength of evidence tables by type of intervention (Table 48 through Table 50).

Population

Of the eight studies, four did not appear to select for asthma severity or control;[115, 117, 120, 121] populations for the remaining four were restricted to moderate-to-severe asthma (two studies),[116, 119] low-to-moderate severity (one study),[118] and poorly controlled asthma (one study).[122]

Interventions

Of the eight studies, five studies that focused on patients as the target of the intervention examined the effectiveness of self-management programs that provide education or other strategies for self-management.[115-119] Three of these five studies used traditional care settings with nurses and other professionals;[116, 118, 119] one employed an interactive voice response system;[115] and one tested combinations of audiotapes and booklets.[117]

The remaining three studies focused on providers and systems in addition to patients.[120-122] Of these three, one study evaluated shared decisionmaking between patients and clinicians[122] and two studies evaluated changes in patient adherence when information delivery systems were altered to provide pharmacists[120] or physicians[121] with patient adherence information. The pharmacist trial also provided patients in the active arms with peak flow monitors and pharmacists in all arms with disease-specific training.[120]

Comparator

Six of the eight studies compared active arms to a control arms characterized as "usual care."[115-119, 121] In two of these studies usual care was minimally described.[115, 119] In the remaining four studies, usual care could be inferred from the description to be a care environment that was unaltered by the intervention with the exception of data collection.[116-118, 121] Data collection for control arms varied: e.g., minimal effort in one study that relied on pharmacy refill data for outcomes[121] to fairly intense efforts in two studies that used daily monitoring of symptoms, medication use, and peak flow data during the intervention period.[116, 118] Usual care also varied in setting and intensity across these six studies.

Another study described the control arm as usual care but provided physicians in the control arm with audio, video, and written materials and tools to discuss adherence.[122] The only trial without a usual care arm involved a pharmacist intervention in which pharmacists in all arms received training.[120] This trial included escalating levels of intervention components: the patients in both active arms received peak flow meters, but patient-specific information about peak flow use was available to pharmacists only in one of two active arms.

Outcome and Timing

No study reported on initiation of therapy. All reported on adherence. Seven of eight studies included percent adherence as a measure, that is, number of doses taken relative to number prescribed. These studies used metered dose inhaler data, pharmacy refill data, or a combination of self-reported adherence and electronic monitoring data to construct the measure, generally using objective measures for the numerator. A single study relied on self-reported measures of adherence alone.[120]

Among the studies that we evaluated for health and other outcomes, the primary morbidity measure was symptom severity or control, using self-report measures. Studies used a wide range of measures and instruments; only two studies used a common instrument (the Asthma Therapy Assessment Questionnaire).[117, 122] One study also evaluated refills of short-acting beta-agonists (SABA) using refill data.[122]

The self-management interventions were generally of short duration, ranging from 4 to 7 weeks. Outcomes were measured at various time points: during the intervention, at the last visit or contact, or shortly after the intervention ended. The shared decisionmaking study recorded 2-year adherence information for an intervention with an active component that lasted 9 months.[122] The two studies of system change recorded medication adherence at 1 year.[120, 121]

Setting

Of the five self-management interventions, four studies were conducted in one or more clinics[115-118] and another recruited directly from the community.[119] Interventions that also focused on providers or the health system recruited local pharmacies in one case,[120] and worked within health systems in the other two.[121, 122]

Applicability

Two studies reported eligibility criteria in poor detail, making judgments about applicability challenging.[115, 117] The remaining studies represent a broad range of severity overall, but the paucity of evidence for some types of interventions limit statements about applicability of findings to subpopulations along the spectrum of severity. The most significant limitation to applicability, particularly for patient-directed self-management interventions, is the lack of long-term outcome data.

Key Points

Self-Management

- Medication adherence: improvement in adherence during or immediately after an intervention is completed (moderate strength of evidence); longer-term effect (insufficient evidence).
- Biomarkers: pulmonary function and inflammation markers (insufficient evidence)
- Symptom improvement: no evidence of benefit (insufficient evidence)
- Quality of life: no benefit (low strength of evidence)

Pharmacist or Physician Access to Patient Adherence Information

- Medication adherence: no improvement in adherence within the first year of initiating treatment (low strength of evidence)

Shared Decisionmaking

- Medication adherence: benefit within the first year of initiating treatment (low strength of evidence)
- Biomarkers: benefit for pulmonary function within the first year of initiating treatment (low strength of evidence)
- Symptom improvement: reduced rescue medication use within 2 years of initiating treatment (low strength of evidence)
- Quality of life: improved quality of life (low strength of evidence)
- Health care utilization: reduced asthma-related visits within the first year of initiating treatment (low strength of evidence)

Other Outcomes for Self-Management, Pharmacist or Physician Access to Patient Adherence Information, and Shared Decisionmaking

- All other outcomes for the interventions listed above: insufficient due to lack of evidence

Detailed Synthesis: Interventions Directed at Patients through Self-Management of Asthma

Medication Adherence

Of the five self-management interventions for asthma that were directed at patients, four showed statistically significant improvement in percent adherence in the intervention arm compared with the control arm (Table 43).[115, 117-119] In the remaining study, percent adherence did not differ significantly, but the odds of adhering to a 60 percent threshold were higher for the

intervention group than the control group at 4 weeks (during the intervention) but not at 14 weeks (after the end of the intervention).[116] Four of five studies limited measurement of outcomes to the end of the intervention period or a month thereafter.[115, 116, 118, 119] The remaining study found that the group receiving a combination of audiotape and booklet had significantly greater adherence than usual care at both 3 and 6 months;[117] the booklet group also had significantly higher adherence than usual care at 6 months. Other measures for this study, such as the number of preventive medication doses missed in the previous 2 weeks, were not significant at 3 or 6 months for any group compared with usual care. The results for this body of evidence, although suggestive of improvement in adherence during the intervention period, offer limited insight on whether improvements in adherence can be sustained over the long term for this chronic disease (Table 48).

Other Outcomes

We evaluated other outcomes for all five studies because all five reported some degree of improvement in medication adherence. Two studies evaluated pulmonary function and some measures of inflammation through a variety of sputum markers (Table 44).[116, 118] Neither found differences between study arms in pulmonary function, although both reported significant improvement in one sputum marker each and acknowledged that the clinical role of these markers was unclear. The five studies reported a wide variety of symptom improvement measures (Table 45); two found no statistically significant improvements in the intervention arm compared with the control arm,[115, 117] and one found a trend toward a higher percentage with symptom-free days in the control arm.[119] In the two studies that reported some statistically significant improvement in the intervention arm compared with the control arm for one measure or time period, no statistically significant differences were found in other measures or at other time points.[116, 118] Four studies evaluated quality of life and found no differences between study arms (Table 46).[115-118] The conclusion of limited or no evidence of effectiveness of these interventions on pulmonary function, symptom improvement, and quality of life needs to be evaluated in the context of the relatively small size and likely underpowered nature of these trials (Table 48).

Detailed Synthesis: Interventions Providing Physicians or Pharmacists Access to Patient Adherence Data for Asthma or Chronic Obstructive Pulmonary Disease

Medication Adherence

Of three interventions aimed at providers and/or systems,[120-122] two focused on patient adherence when providers (pharmacists or physicians) were provided with patient adherence data (Table 43).[120, 121] The pharmacist intervention, which provided additional elements of pharmacist care, examined the effects of this intervention separately for patients with asthma or COPD.[120] Neither trial found statistically significant differences between groups at 1 year following the commencement of the study, suggesting evidence of no benefit (Table 49). The other trial, which evaluated shared decisionmaking or clinical decisionmaking compared with usual care, found statistically significant differences in medication adherence at 1 year; clinical decisionmaking was more effective than usual care, and shared decisionmaking was more effective than either clinical decisionmaking or usual care.[122] At 2 years, clinical decisionmaking was no longer significantly different than usual care but shared decisionmaking continued to produce

statistically significant improvements in medication adherence compared with clinical decisionmaking or usual care.

Other Outcomes

One trial reported significantly improved pulmonary function for the shared decisionmaking group alone compared with usual care (Table 44), suggesting evidence of benefit (Table 50).[122] Both interventions' arms had higher odds of reporting no asthma control problems at 1 year than did the group receiving usual care, and both reported significantly lower acquisition of short-acting beta agonists ([SABA] total days' supply acquired in a year/365 days) compared with usual care at 1 year (Table 45). At 2 years, only the shared decisionmaking arm reported lower SABA use than usual care. Both clinical- and shared- decisionmaking arms resulted in significantly higher quality of life (Table 46) and fewer asthma-related visits than usual care (Table 50).

Table 42. Medication adherence interventions for reactive airway diseases: study characteristics

Author, year N at Randomization	Population Setting	Intervention and Comparator
Bender et al., 2010[115] N=50	Adults ages 18-65 Tertiary care center	G1: At least two interactive-voice-response phone calls to monitor symptoms and encourage adherence G2: Usual care (not described)
Berg et al., 1997[119] N=55	Adults > 18 Setting not specified, held in the community	G1: Six face-to-face sessions on asthma education, self-management behaviors, relaxation techniques, problem-solving skills G2: Usual care with physician
Janson et al., 2003[118] N=65	Adults ages 18-55 Clinic laboratory	G1: Asthma education, skills for correct medication inhalation and peak-flow meter use; peak-flow data reported to patients; written asthma action plan; patients maintained daily diary of symptoms, peak flow, and medication use G2: Usual care: all questions referred to regular physician; no explicit education or instruction about asthma; no feedback on peak-flow data patients maintained daily diary of symptoms, peak flow, and medication use
Janson et al., 2009[116] N=84	Adults ages 18-55 Community clinics	4-week run on inhaled corticosteroid therapy for all patients G1: Individualized self-management education; patients maintained daily diary of symptoms, peak flow, and medication use G2: Usual care with self-monitoring alone; patients maintained daily diary of symptoms, peak flow, and medication use
Schaffer et al., 2004[117] N=46	Population, setting NR	G1: 30-minute audiotape story following a protagonist through asthma diagnosis and care; educational booklet G2: Audiotape alone G3: Educational booklet alone G4: Usual care: Patient receives standard education from provider

Table 42. Medication adherence interventions for reactive airway diseases: study characteristics (continued)

Author, year N at Randomization	Population Setting	Intervention and Comparator
Weinberger et al., 2002[120] N= 36 Pharmacies; 1,113 Patients	Adults > 18 Pharmacy	G1: Pharmaceutical care program: pharmacists were given access to patient-specific data for peak expiratory flow rate (PEFR), emergency department visits and hospitalizations, recent medications and compliance. Pharmacists were trained on how to access and interpret patient-specific information and were educated about reactive airway disease. Incentives were provided for high utilization of patient-specific data. Patients were given peak-flow monitors, instructions about its use, and monthly calls to obtain PEFR results. G2: Peak flow monitoring: pharmacists were educated about diabetes, hypertension, and reactive airway disease. Patients were given peak-flow monitors and monthly reminders to use peak-flow monitors. Pharmacists were not provided with patient-specific data. G3: Usual care: pharmacists were educated about diabetes, hypertension, and reactive airway disease. Patients were not given peak-flow monitors.
Williams et al., 2010[121] N=207 Providers; 2,698 Patients	Primary care providers; Patients ages 5-56 Primary care clinics	G1: Physicians receive electronic adherence data for their patients every 2 weeks G2: Usual care with educational tools for providers to discuss nonadherence with their patients
Wilson et al., 2010[122] N=612	Adults ages 18-70 Kaiser Permanente medical centers	G1: Shared decisionmaking model for two face-to-face visits and three phone calls G2: Clinical decisionmaking model for two face-to-face visits and three phone calls G3: Usual care: stepped approach to medications

Abbreviations: G, group; N, number; NR, not reported; PEFR, peak expiratory flow rate.

Table 43. Interventions for reactive airway diseases: medication adherence outcomes

Study N Analyzed for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
Bender et al., 2010 [115] G1: 25 G2: 25	Percent adherence: (taken: prescribed) Electronic monitors and dose counters; change in canister weight if needed/nonself-report	Percent at 10 weeks, Mean (SD): G1: 64.5 (17.2) G2: 49.1 (16.8) 95% CI, NR F: 9.66 p=0.0032
Berg et al., 1997 [119] G1: 31 G2: 24	Percent adherence (taken: prescribed) Measured by monitored inhaler and self-reported prescription information/nonself-report	Mean (SD) at 7 weeks G1: 49 (31) G2: 32 (28) 95% CI, NR p<0.05
Janson et al., 2003 [118] G1: 33 G2: 32	Percent adherence (taken: prescribed) Self-report, supplemented by medication monitors/nonself-report	Mean percent (SD) over 7 weeks: G1: 91 (32) G2: 62 (38) 95% CI, NR Between-group difference from baseline to 7 weeks, Mean (95% CI): 24 (5-43) p=0.01

Table 43. Interventions for reactive airway diseases: medication adherence outcomes (continued)

Study N Analyzed for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
Janson et al., 2009 [116] G1: 45 G2:39	Percent adherence: (taken: prescribed) Electronic metered devices/nonself-report	Mean change in percent at 4 weeks: G1: -0.18 G2: -1.40 95% CI, NR p=0.72 Mean change in percent at 14 weeks: G1: -4.28 G2: -4.14 95% CI, NR p=0.97
	Odds of maintaining greater than 60% adherence Electronic metered devices/nonself-report	Odds at 4 weeks, compared with baseline: G1: 9.2 G2: 0.4 95% CI, NR p=0.02 Odds at 14 weeks, compared with 4 weeks: G1: 0.3 G2: 1.1 95% CI, NR p=0.31
Schaffer et al., 2004 [117] G1: 11 G2: 10 G3: 12 G4: 13	Percent adherence (days of medication dispensed/number of days between refill and date of study visit) for previous 3 months. Pharmacy refill data/nonself-report	Mean (SD) at baseline: G1: 0.41 (0.42) G2: 0.32 (0.39) G3: 0.62 (0.34) G4: 0.62 (0.40) Mean (SD)—p-value compared with G4 at 3 months: G1: 0.53 (0.41)—p=0.07 G2: 0.40 (0.32)—p=0.4 G3: 0.73 (0.23)—p=0.02 G4: 0.42 (0.39) 95% CI, NR Mean (SD)—p-value compared to G4 at 6 months: G1: 0.77 (0.24)—p=0.04 G2: 0.48 (0.38)—p=0.17 G3: 0.77 (0.24)—p=0.02 G4: 0.40 (0.44) 95% CI, NR
	Number of doses of preventive medication missed in previous 2 weeks Self-report/nonself-report	Not significant for any group

Table 43. Interventions for reactive airway diseases: medication adherence outcomes (continued)

Study N Analyzed for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
Weinberger et al., 2002 [120] G1: 356 G2: 296 G3: 246	Proportion of noncompliance Self-report	Adjusted OR (95% CI) at 1 year G1-G2: aOR: 0.81 (0.58 to 1.12) G1-G3: aOR: 1.09 (0.80 to 1.49)
	Morisky 4-item scale for medication compliance range from 0 (low) to 4 (high) Self-report	Mean scores (SD) at 1 year: G1: 0.87 (0.05) G2: 0.85 (0.05) G3: 0.92 (0.06) 95% CI, NR p=0.57
Williams et al., 2010 [121] G1: 1335 G2: 1363 (N randomized)	Percent adherence as a continuous measure of medication availability Electronic prescription information and pharmacy claims data/nonself-report	Mean (SE) for 12 months: G1: 21.3 (2.5) G2: 23.3 (2.2) 95% CI, NR p=0.553
Wilson et al., 2010 [122] G1: 204 G2: 204 G3: 204	Medication acquisition ratio for all asthma medications (total days' supply acquired in a year/365 days) Pharmacy refill data/nonself-report	Means at 1 year: G1: 0.67 G2: 0.59 G3: 0.46 (95% CIs): G1-G3: (0.13 to 0.280), p=0.0001 G1-G2: (0.01 to 0.15), p=0.0029 G2-G3: (0.05 to 0.20), p=0.0008 Mean differences at 2 years: G1-G3: 0.03 G1-G2: 0.04 G2-G3: -0.01 (95% CIs): G1-G3: (-0.05 to 0.11) G1-G2: (-0.04 to 0.12) G2-G3: (-0.09 to 0.07)
	Medication acquisition ratio for inhaled corticosteroids (total days' supply acquired in a year/365 days) Pharmacy refill data/nonself-report	Means at 1 year G1: 0.59 G2: 0.52 G3: 0.37 (95% CIs):NR p: G1-G3, 0.0001 G1-G2, 0.017 G2-G3, 0.0001

Table 43. Interventions for reactive airway diseases: medication adherence outcomes (continued)

Study N Analyzed for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
	Acquisition of beclomethasone canister equivalents Pharmacy refill data/nonself-report	Means at year 1: G1: 10.9 G2: 9.1 G3: 5.2; (95% CIs): G1-G3: (4.5 to 7.0), p=0.0001 G1-G2: (0.57 to 0.31), p=0.005 G2-G3: (2.6 to 5.2), p=0.0001 Means at year 2: G1: 7.1 G2: 5.8 G3: 4.6 (95% CIs): G1-G3: (1.2 to 3.8), p=0.0002 G1-G2: (0.04 to 2.7), p=0.04 G2-G3 (-0.18 to 2.4), p>0.05
Year 1: G1: 40 G2: 44 G3: 52 Year 2 G1: 112 G2: 108 G3: 59	Medication acquisition for long-acting beta-agonists Pharmacy refill data/nonself-report	Mean difference at 1 year: G1-G3: 0.11 G1-G2: 0.09 G2-G3: 0.01 (95% CIs): G1-G3: (0.02 to 0.20) G1-G2: (0.02 to 0.17) G2-G3: (-0.08 to 0.11) Mean difference at 2 years: G1-G3: 0.11 G1:G2: 0.09 G2-G3: 0.01 (95% CIs): G1-G3: (0.01 to 0.20) G1-G2: (0.01 to 0.18) G2-G3: (-0.08 to 0.11)

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; G, group; NR, not reported; OR, odds ratio; SD, standard deviation; SE, standard error.

Table 44. Medication adherence interventions for reactive airway disease: biomarker percentage forced expiratory volume in one second (FEV1%)

Author, Year N in Each Group	Outcome Source/Method	Results
Janson et al., 2003 [118] G1: 33 G2: 32	FEV1% Spirometry	Group difference (95% CI) from baseline to 7 weeks: G1: 90 (16) G2: 80 (20) Between group difference: 5 (-1 to 10) 95% CI, NR p=0.09
Janson et al., 2009 [116] G1: 45 G2:39	Mean change in FEV1% Spirometry	From 0-4 weeks G1: 1.47 G2: 2.72 p=0.32 From 4-14 weeks G1:1.13 G2: -0.37 p=0.25 From 0-14 weeks G1:2.60 G2: 1.13 p= 0.25 95% CI, NR
Wilson et al., 2010 [122] G1: 182 G2: 180 G3: 189	FEV1% Spirometry	Means at 1 year: G1: 76.5% G2: 75.8% G3: 73.1% (95% CIs): G1-G3: (NR), p=0.0068 G1-G2: (NR), p=0.47 G2-G3: (NR), p=0457
	FEV1:FEV6 ratio Spirometry	Means at 1 year: G1: 72.8% G2: 71.8% G3:70.0% (95% CIs): G1-G3: (NR), p=0.0005 G1-G2: (NR), p=0.09 G2-G3: (NR), p=0.07

Abbreviations: CI, confidence interval; FEV1%, forced expiratory volume in one second; FEV6, forced expiratory volume in 6 seconds; G, group; NR, not reported.

Table 45. Medication adherence interventions for reactive airway diseases: morbidity

Author, Year N in Each Group	Outcome Source/Method	Results
Bender et al., 2010[115] G1: 25 G2: 25	Asthma control ACT 5 items; Range NR (higher score =better)	Mean change (SD) in ACT score at 10 weeks G1: 1.120 (3.90) G2: 1.840 (4.14) 95% CI, NR p=0.530
Berg et al., 1997[119] G1: 31 G2: 24	Symptoms per day Daily journal recording the presence or absence of 4 symptoms	Mean (SD) at week 7: G1: 1.1 (0.91) G2: 0.85 (0.93) 95% CI, NR p: Not significant
	Percent symptom-free days Daily journal recording the presence or absence of 4 symptoms	Mean (SD) at week 7: G1: 44 (38) G2: 60 (37) 95% CI, NR p<0.1
Janson et al., 2003[118] G1: 33 G2: 32	Symptom severity Severity of Asthma Symptoms scale Items: NR; Range 0-10 (lower score=better)	Group difference (95% CI) from baseline to 7 weeks: G1: 8 (7) G2: 7 (6) Between group change: -0.9 (-4 to 2) p=0.56
	Perceived asthma control PCAQ 11 items; Range NR (directionality NR)	Group difference (95% CI) from baseline to 7 weeks: G1: 42 (5) G2: 42 (5) Between group difference: 2.6 (0.1 to 5) p=0.04
Janson et al., 2009[116] G1: 45 G2:39	Frequency of nighttime awakenings Daily self-report	Odds ratios: From 0-4 weeks G1: 0.2 G2: 0.7 p=0.13 From 4-14 weeks: G1: 0.7 G2: 1.2 p=0.45 From 0-14 weeks G1: 0.2 G2: 0.8 p=0.03 95% CI, NR
	Symptom-free days Daily self-report	Odds ratios From 0-4 weeks G1: 2.2 G2:1.6 p=0.48 From 4-14 weeks G1: 2.7 G2: 1.8 p=0.63

Table 45. Medication adherence interventions for reactive airway diseases: morbidity (continued)

Author, Year N in Each Group	Outcome Source/Method	Results
		From 0-14 weeks G1: 5.9 G2: 2.8 p=0.51 95% CI, NR
	Symptom severity Symptom severity scale Items NR; Range 0-10 (lower score=better) Daily self-report	Mean change in symptom score: From 0-4 weeks G1: -1.28 G2: -1.41 p=0.84 From 4-14 weeks G1: -0.97 G2: 0.11 p=0.06 From 0-14 weeks: G1: -2.25 G2: -1.30 p=0.19 95% CI, NR
	Beta-agonist use Pharmacy refill data	Incidence ratios: From 0-4 weeks G1: 0.6 G2: 0.8 p=0.01 From 4-14 weeks G1: 0.5 G2: 0.5 p=0.98 From 0-14 weeks G1: 0.3 G2: 0.4 p=0.3 95% CI, NR
Schaffer et al., 2004[117] G1: 11 G2: 10 G3: 12 G4: 13	Asthma control Asthma Control Questionnaire 7 items; Range NR (lower score =better)	Mean (SD) G1: 1.10 (0.58)—p: NS; text does not clearly indicate comparator G2: 1.62 (1.04)—p=0.6 for G2 vs. G4 G3: 1.39 (1.0)—p: NS; text does not clearly indicate comparator G4: 1.71 (1.18) 95% CI, NR Mean(SD): G1: 1.30 (0.76)—p: NS; text does not clearly indicate comparator G2: 1.47 (1.14)—p=0.4, for G2 vs. G4 G3: 1.30 (0.76)—p: NS; text does not clearly indicate comparator G4: 1.25 (1.07) 95% CI, NR

Table 45. Medication adherence interventions for reactive airway diseases: morbidity (continued)

Author, Year N in Each Group	Outcome Source/Method	Results
	Asthma control PCAQ 11 items; Range NR (higher score=better)	Mean (SD)—p-values reflect comparisons with G4 at 3 months: G1: 49.90 (4.6)—p=0.6 G2: 44.0 (4.97)—p=0.8 G3: 45.75 (6.27)—p=0.3 G4: 44.67 (6.82) 95% CI, NR Mean(SD)—p values reflect comparisons with G4 at 6 months: G1: 43.33 (14.43)—p=0.8 G2: 44.20 (6.16)—p=0.4 G3: 43.33 (14.44)—p=0.2 G4: 45.27 (5.57) 95% CI, NR
Wilson et al., 2010 [122] G1: 182 G2: 180 G3: 189	Asthma control in previous 4 weeks ATAQ 4 items; Range NR (lower score=better) No asthma control problems (ATAQ score=0)	Mean change in ATAQ score at 1 year G1: -0.80 G2: -0.54 G3: -0.46 95% CI, NR p: NR OR (95% CI) at 1 year G1 vs. G3: 1.9 (1.3-2.9) 95% CI, NR p=0.002 G2 vs.G3: 1.6 (1.1-2.4) 95% CI, NR p=0.0239
G1: 204 G2: 204 G3: 204	Mean equivalents of SABA acquired Pharmacy refill data	Means in Year 1: G1: 6.5 G2: 7.1 G3:8.1 G1-G3: p=0.002 G1-G2: p=0.09 G2-G3: p=0.038 95% CI, NR Means in Year 2: G1: 4.7 G2: 6.0 G3: 6.3 G1-G3: p=0.0141 G1-G2: p=0.06 G2-G3: p>0.05 95% CI, NR

Abbreviations: ACT, Asthma Control Test; ATAQ, Asthma Therapy Assessment Questionnaire; CI, confidence interval; G, group; NR, not reported; NS, not significant; OR, odds ratio; PCAQ, Perceived Control of Asthma Questionnaire; SABA, short-acting beta-agonists; SD, standard deviation.

Table 46. Medication adherence interventions for reactive airway diseases: quality of life

Author, Year N in Each Group	Outcome Source/Method	Results
Bender et al., 2010 [115] G1: 25 G2: 25	Quality of life AQLQ 32-items; Range NR (higher score=better)	Mean change in score (SD) at 10 weeks G1: -0.152 (0.92) G2: -0.381 (1.06) p=0.419
Janson et al., 2003 [118] G1: 33 G2: 32	Quality of life Asthma-related quality of life scale Items: NR; Range NR (directionality NR)	Group difference (95% CI) from baseline to 7 weeks: G1: 17 (9) G2: 19 (13) Between group difference: -4.4 (-9 to 0.2) p=0.06
Janson et al., 2009 [116] G1: 45 G2:39	Quality of life Quality of life questionnaire Items NR; Range 0-80 (lower score=better)	Mean change in QOL score From 0-4 weeks: G1: -2.71 G2: -1.39 95% CI, NR p=0.36 From 4-14 weeks G1: -1.11 G2: 0.58 95% CI, NR p=0.27 From 0-14 weeks G1: -3.82 G2: -0.80 95% CI, NR p=0.06
Schaffer et al., 2004 [117] G1: 11 G2: 10 G3: 12 G4: 13	Asthma-related quality of life in preceding 2 weeks Mini-AQLQ 15-items; Range NR (higher score=better)	Mean (SD), p-values reflect comparisons with G4 at 3 months: G1: 5.15 (0.91), p=0.3 G2: 4.94 (0.97), p=0.5 G3: 5.13 (1.32), p=0.6 G4: 4.68 (1.49) 95% CI, NR Mean(SD), P values reflect comparisons with G4 at 6 months: G1: 5.22 (0.99), p=0.8 G2: 5.30 (0.8), p=0.4 G3:5.22 (0.98), p=0.2 G4: 4.87 (1.2) 95% CI, NR
Wilson et al., 2010 [122] G1: 182 G2: 180 G3: 189	Quality of life Symptom Subscale of the (Mini AQLQ 5 items; Range NR (higher score=better)	Mean symptom subscale scores at year 1 G1: 5.5 G2: 5.4 G3: 5.1 95% CI, NR G1-G3: p=0.0003 G1-G2: p>0.05 G2-G3: p=0.0009

Abbreviations: AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; G, group; Mini-AQLQ, Mini-Asthma Quality of Life Questionnaire; NR, not reported; QOL, quality of life; SD, standard deviation.

Table 47. Medication adherence interventions for asthma: healthcare utilization

Author, Year N in Each Group	Outcome Source/Method	Results
Wilson et al., 2010 [122] G1: 204 G2: 204 G3: 204	Number of asthma-related visits per year Electronic medical records	Means at 1 year postrandomization: G1: 1.0 G2: 1.1 G3: 1.4 (95% CI): G1-G3: (-0.66 to -0.07), p=0.0161 G1-G2: (-0.29-0.30), p=0.97 G2-G3: (-0.67-0.07), p=0.0147

Abbreviations: CI, confidence interval; G, group.

Table 48. Asthma: strength of evidence for education and self-management interventions

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Study Design/ Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Asthma education and self-management vs. usual care	5; 303 (300)	Medication adherence	RCT Medium	Consistent	Direct	Imprecise	Difference in percentage points for adherence: 14-31 (range) Moderate SOE of benefit for duration of intervention Insufficient for longer-term effects
	0	Mortality	NA	NA	NA	NA	Insufficient
	2; 152 (149)	Pulmonary function	RCT Medium	Consistent	Indirect	Imprecise	Insufficient
	2; 152 (149)	Inflammation markers	RCT Medium	Inconsistent	Indirect	Imprecise	Insufficient
	5; 303 (300)	Symptom improvement	RCT Medium	Inconsistent (trend to improvement sometimes favors intervention arm and sometimes control arm)	Direct	Imprecise	Varied measures and magnitude Insufficient
	4; 248 (245)	Quality of life	RCT Medium	Consistent	Direct	Imprecise	Varied measures and magnitude Low SOE of no benefit
	0	Patient satisfaction	NA	NA	NA	NA	Insufficient
	0	Healthcare utilization	NA	NA	NA	NA	Insufficient
	0	Quality of care	NA	NA	NA	NA	Insufficient

Abbreviations: NA, not applicable; RCT, randomized controlled trial; SOE, strength of evidence.

Table 49. Asthma: strength of evidence for interventions providing physicians or pharmacists access to patient adherence data

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Study Design/ Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Information systems change vs. usual care	2; 3,811 (3,596)	Medication adherence	RCT Low	Consistent	Direct	Precise	2 percentage points difference in percent adherence; 0.5-0.7 difference in Morisky scale Low SOE of no benefit
	0	Mortality	NA	NA	NA	NA	Insufficient
	0	Biomarkers	NA	NA	NA	NA	Insufficient
	0	Symptom improvement	NA	NA	NA	NA	Insufficient
	0	Quality of life	NA	NA	NA	NA	Insufficient
	0	Patient satisfaction	NA	NA	NA	NA	Insufficient
	0	Healthcare utilization	NA	NA	NA	NA	Insufficient
	0	Quality of care	NA	NA	NA	NA	Insufficient

Abbreviations: NA, not applicable; RCT, randomized controlled trial; SOE, strength of evidence.

Table 50. Asthma: strength of evidence for shared decisionmaking interventions

Intervention	Number of Studies; Subjects (Analyzed)*	Outcome	Study Design/ Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Shared decision-making vs. usual care	1; 612 (612)	Medication adherence	RCT Medium	Unknown	Direct	Precise	Difference in medication acquisition ratio for all asthma medications: 0.13-0.21 (range) Low SOE of benefit
	0	Mortality	NA	NA	NA	NA	Insufficient
	1; 612 (551)	Pulmonary function	RCT Medium	Unknown	Direct	Precise	Difference in FEV1 percentage points: 2.7-3.4 Low SOE of benefit
	0	Inflammation markers	NA	NA	NA	NA	Insufficient
	1; 612 (612)	Symptom improvement	RCT Medium	Unknown	Direct	Precise	Difference in mean equivalents of SABA acquired at 2 years between shared decisionmaking and usual care: 1.6 Low SOE of benefit
	1; 612 (551)	Quality of life	RCT Medium	Unknown	Direct	Precise	Difference in subscale scores on 5-item Mini Asthma Quality of Life Questionnaire: 0.3-0.4 Low SOE of benefit
	0	Patient satisfaction	NA	NA	NA	NA	Insufficient
	1; 612 (612)	Healthcare utilization	NA	Unknown	Direct	Precise	Difference of 0.3-0.4 fewer asthma-related visits per year Low SOE of benefit
	0	Quality of care	NA	NA	NA	NA	Insufficient

Abbreviations: NA, not applicable; RCT, randomized controlled trial; SOE, strength of evidence.

Key Question 1. Depression: Medication Adherence Interventions

Description of Included Trials

Overview

We found 12 randomized controlled trials (RCTs) (reported in 15 articles) on depression[83, 84, 97, 123-134] (Table 51).

These trials varied along numerous dimensions including the presence of other chronic conditions, type of depression (e.g., new episode, ongoing episode [with unspecified recency or all depression], recurrent depression), primary target of the intervention (patient, provider, systems, or combinations), and the type of intervention. We used the type of intervention as the primary means of clustering studies for the detailed synthesis and then incorporated other dimensions of study characteristics within these intervention clusters. We rated one trial as having low risk of bias[134] and all others as having medium risk of bias. Table 51 provides summary information about the trials' intervention characteristics. Table 52 through Table 58 present results for medication adherence and other outcomes. Table 59 through Table 62 present strength-of-evidence grades.

Population

Two trials focused on patients with both depression and diabetes,[83, 84] one on patients with depression and hypertension,[97] and one on patients with depression and HIV.[133] Eight trials did not specify that subjects had any chronic conditions other than depression[123-132, 134] (Table 51).

The 12 trials covered a range of clinical presentations, although none was entirely among new patients, that is, patients with a first-ever diagnosis of depression. Six trials focused on patients with a new episode (defined as no use of antidepressants for a specified length of time ranging from 3 to 6 months before the index episode), but these either included some patients with recurrent depression or did not specify recurrence status.[123-128, 131, 132, 134] Of these, one trial (reported in multiple articles) specifically limited the population further to patients who had recurrent depression, dysthymia, and a high risk of relapse but who had largely recovered after 8 weeks of antidepressant treatment.[125-127] Six trials did not require a new episode of depression as a condition of inclusion.[83, 84, 97, 129, 130, 133] Two provided data separately for major and minor depression.[129, 130] Another trial distinguished between moderate-severity and high-severity depression.[131, 132]

Intervention

Of the 12 trials, two used interventions that appeared to be directed primarily at patients and providers. These two trials did not appear to require systems changes to be implemented in other settings;[123, 124] they involved telephone monitoring but differed in the extent to which the effort involved feedback loops to other providers. The less intense intervention, characterized as telemonitoring, involved pharmacists monitoring adherence and providing education in three telephone calls; pharmacists contacted providers only as needed.[123] In the more intense intervention, characterized as telephone case management, care managers relied on three telephone calls to patients to monitor adherence; in addition, care managers routinely communicated findings to the treating psychiatrist and coordinated care for patients.[124] This intervention was directed to patients with new episodes of depression, that is, no regular

antidepressant use in the past 4 months.[123, 124] The authors did not clarify whether patients had recurrent depression.

Three case management interventions were primarily directed at patients and providers. Because they were conducted in populations with multiple chronic conditions or in depressed patients in a primary care setting, they required some degree of systems integration in team care. Two interventions, conducted by the same team, were identical in process with the exception of the coexisting chronic disorder (diabetes in one case[84] and hypertension in the other[97]). These two trials did not specify the nature of the depressive episode: they required only a diagnosis of depression in the past year. In addition to telephone calls and care coordination activities, all case management interventions included multiple regular in-person visits.[84, 97] A third trial, focusing on relapse prevention, was limited to patients with recurrent depression.[125-127]

Six trials focused on collaborative care models that required system-level changes.[83, 128-133] These interventions were all multifaceted and involved close collaboration among various health care providers and a team care approach. Patients received education, monitoring, and counseling. Five of these interventions included either specific courses of therapy[129, 130] or stepped approaches to care and included in-person visits in the intervention arm.[83, 131-133] The remaining trial in this category did not include therapy specifically, but the pharmacists providing followup over numerous telephone calls facilitated appointments with mental health providers.[128]

The final systems-level intervention examined the effect of the use of information systems in a health maintenance organization to trigger monthly lists of nonadherent patients to providers and monthly letters to nonadherent patients.[134] This trial limited patients to those on newly prescribed therapy, that is, patients with no history of previous antidepressant use for 6 months before the index episode. The proportion with recurrent depression was not specified.

Comparator

Comparators for all interventions included usual care, although as with the intervention, the intensity of usual care varied. The telemonitoring, case management, and information systems interventions generally reported usual care as routine care offered in that setting.[84, 97, 123, 124] The collaborative care interventions also used usual care as the comparator,[83, 128-133] but usual care was specified as involving depression care by primary care physicians, including antidepressants and referrals to specialty mental health services when needed.[83, 129-133]

Outcomes and Timing

Medication adherence outcomes differed markedly across these trials. Very few reported the same outcome; several reported multiple outcomes. No trial reported on initiation of therapy. One trial reported on persistency.[134] Medication adherence outcomes examined in the other trials included the following: whether the prescription was filled at successive time points;[125-127] dichotomous measures of adherence (taken: prescribed), using thresholds of 80 percent or higher[84, 97, 133] and 95 percent or higher;[133] dichotomous measures of adequate doses (based on strength and number of doses according to guidelines) taken for a minimum number of days over a given period (e.g., 90 days of adequate dose over 6 months);[131, 132] dichotomous measures of gap days (e.g., less than 10 days over 30 days);[134] and continuous measures of days nonadherent[83] or doses omitted[123] over a given period of time. Two trials relied solely on self-reported measures of adherence;[128, 133] all others used pharmacy refill or pharmacy claims data[83, 123-127, 129-132, 134] or medication event monitoring systems (MEMS).[84, 97] For length of followup,

medication adherence outcomes were reported at times ranging from 6 weeks to 28 months after randomization of patients in the trials.

Of the trials for which we report health and other outcomes, two with very similar designs reported on symptom improvement using the same scale: the Center for Epidemiologic Studies-Depression scale (CES-D).[84, 97] Three others used symptom improvement on the Hopkins Symptom Checklist (SCL-20);[125-127, 129, 131, 132] these three trials used other measures of symptom improvement as well. Two trials evaluated similar measures along a scale for patient satisfaction, that is, rating care as good to excellent.[129, 131, 132] One trial also reported on healthcare utilization and costs.[129, 131, 132]

Most trials reported on outcomes during, immediately following, or within 3 months of the end of the intervention, with intervention length ranging from 4 weeks[84, 97] to 12 months.[83, 125-128, 133] Some 12-month interventions included an acute phase for the first 3 months or so, followed by a continuation phase that lasted up to 12 months.[83, 128] Only one trial reported on long-term outcomes (up to 28 months after randomization); the active phase of this intervention occurred for a maximum of 3 months.[131, 132] For measures that were constructed based on gap days or days adherent divided by the total number of days prescribed, the look-back period for the denominator varied from 4 days to 1 year, with 3 months or 6 months being the two most commonly used reference time periods.

Setting

Nine trials were set in primary care clinics: of these, two were in community-based primary care,[84, 97] one was in university-based primary care clinics,[128] and six were in primary care clinics in one health care system (Group Health Cooperative).[83, 124-127, 129-132] Of the remaining trials, one was set in community pharmacies affiliated with a managed care organization;[123] one was in a Department of HIV clinic of the Department of Veterans Affairs (VA);[133] and one employed systems records within a large health maintenance organization.[134]

Applicability

The body of evidence for depression, despite the replication of collaborative care interventions in multiple trials, is somewhat limited in applicability for collaborative care and case management interventions in particular. In both instances, the same team produced multiple studies, leaving uncertain the degree to which their successes can be replicated by other teams.

Key Points

Overview

- Twelve trials produced mixed evidence on medication adherence.
- Five of 12 trials reported improvement in health and other outcomes.

Medication Telemonitoring or Telephone Care

- Medication adherence: Telephone-only interventions with low intensity and short duration showed no statistically significant benefit (insufficient evidence).

Case Management

- Medication adherence: Case management improved medication adherence for antidepressants (moderate strength of evidence).

- Biomarkers: Case management improved hemoglobin A1C over the short term (low strength of evidence); evidence was insufficient for longer-term outcomes.
- Morbidity:
  - Case management improved diastolic and systolic blood pressure over the short term (low strength of evidence); evidence was insufficient for longer-term outcomes.
  - Case management improved symptoms of depression (moderate strength of evidence).
  - Case management had no statistically significant effect on self-reported disability (evidence was insufficient).

Collaborative Care

- Collaborative care interventions varied by intensity and population; the strength-of -evidence grades reflect these underlying sources of heterogeneity.
- Medication adherence:
  - Intensive collaborative care with multifaceted telephone and in-person components improved medication adherence for (moderate strength of evidence).
  - Telephone-only collaborative care showed no statistically significant improvement in medication adherence (evidence was insufficient).
  - No statistically significant difference in medication adherence was found for patients with depression and HIV or depression and diabetes (strength of evidence was insufficient).
- Morbidity:
  - Collaborative care reduced depressive symptoms in patients with major depression (low strength of evidence).
  - Collaborative care did not result in statistically significant improvement in depressive symptoms for patients with minor depression (insufficient strength of evidence).
  - Collaborative care reduced depressive symptoms for patients with moderately severe depression (low strength of evidence).
- Patient satisfaction:
  - Collaborative care resulted in improved patient satisfaction with antidepressants (low strength of evidence).
- Health care utilization:
  - Evidence was insufficient for primary care or mental health visits.
  - Evidence was also insufficient for total, ambulatory, depression, and nondepression costs.
- Quality of care: Collaborative care resulted in improved patient satisfaction with quality of care (moderate strength of evidence)

Reminders to Nonadherent Patients and Lists of Nonadherent Patients to Providers

- Medication adherence: Reminder letters to nonadherent patients and monthly lists of nonadherent patients to provider, improved patients' medication adherence (low strength of evidence).

Other Interventions and Outcomes

- Evidence was insufficient for all other outcomes.

Detailed Synthesis: Telemonitoring or Telephone Case management Interventions for Depression

Medication Adherence

Neither of the two trials relying solely on telephone-based care found statistically significant differences between intervention and usual care arms on patient adherence (Table 52).[123, 124] The evidence is insufficient for the effects of telephone-only interventions with low intensity and short duration for medication adherence (Table 59).

Other Outcomes

Because neither demonstrated improvement in medication adherence, we did not evaluate data for other outcomes.

Detailed Synthesis: Case Management Interventions for Depression

Medication Adherence

All three interventions using case management demonstrated statistically significant differences between intervention arms and usual care in medication adherence outcomes (Table 52). [84, 97, 125-127] The results for this body of evidence suggest that case management yields improvements in medication adherence during or shortly after the intervention ends (moderate strength of evidence; Table 60). No evidence is available to evaluate the utility of this intervention for improving medication adherence over the longer term (after completion of the intervention).

Other Outcomes

All three trials reporting improvement in medication adherence also reported health and other outcome data. The two 4-week interventions reported outcomes at 6 weeks,[84, 97] and the 12-month intervention reported outcomes 3, 6, 9, and 12 months. All three trials demonstrated significant differences at followup favoring the intervention arm over the control arm for symptoms of depression (Table 54).[84, 97, 125-127] One trial, on relapse prevention, also evaluated three disability measures, using the Medical Outcomes Study Short Form-36 (SF-36) Social Function scale, the SF-36 Emotional Function Scale, and the Sheehan Disability Scale.[125-127] Only one of these three measures (the SF-36 Social Functioning scale) demonstrated a significant difference between intervention and control arm (Table 54).[125-127] This evidence is insufficient to draw conclusions about the effectiveness of case management to improve self-reported disability outcomes.

One trial, conducted among patients with depression and hypertension, reported statistically significant differences between arms (favoring the intervention) in systolic and diastolic blood pressure values at 6 weeks after randomization;[97] another trial reported a statistically significant difference between arms (favoring the intervention) in hemoglobin A1c values at 14 weeks (after the end of the intervention) (Table 53), suggesting low strength of evidence of benefit (Table 60).[84] The trials did not report mortality, patient satisfaction, healthcare utilization, or costs.

Detailed Synthesis: Collaborative Care Interventions for Depression

Medication Adherence

The six included collaborative care interventions varied by population and components. Of the six collaborative care interventions, two focused on providing populations with interventions for depression and another chronic condition (HIV[133] and diabetes[83]) (Table 52). Both offered stepped interventions; for the diabetes trial, the first step involved a choice of psychotherapy or pharmacotherapy.[83] This diabetes trial presented data on adherence to oral glycemics, lipid-lowering agents, and angiotensin-converting enzyme (ACE) inhibitors; antidepressant adherence rates were endogenous to the treatment pathway chosen by the patient and were not presented. The HIV trial reported on adherence to both HIV medications and antidepressants; the look-back period of the patient-reported adherence measure was very short at 4 days.[133] These trials generally showed no statistically significant effect of the intervention arm on medication adherence for most drugs evaluated (antidepressants, HIV medication, oral hypoglycemic, and hypertensive medicines); for one medication (oral hypoglycemic), the intervention arm had significantly worse adherence than usual care.[83]

A third trial relied on pharmacists as the central agents in a collaborative care intervention; they communicated with a care team and had responsibility for numerous activities including prescriptive authority "for the initiation, adjustment, management, and monitoring of pharmacotherapy; triage and care of acute patient problems over the phone; and smoking cessation, blood pressure monitoring, and disease management."[128] Their interaction with patients was limited to weekly phone calls in the first 4 weeks, biweekly calls through week 12, and bimonthly calls from months 4 to12. This intervention showed no difference between intervention and usual care arms in medication adherence at 3, 6, 9, or 12 months. The evidence for these three interventions is insufficient to judge their effectiveness (Table 61).

The three other collaborative care interventions were developed and implemented by investigators common to all three trials and carried out in similar settings. They differed, however, in structure (stepped care with the number of contacts and course of treatment tailored to the patient[131, 132] versus a common protocol for all patients[129, 130]) and process (alternate visits to psychiatrists and primary care[129] versus psychiatrists[131, 132] or psychologists[130] serving as central agent of delivery of the intervention). Two of these trials were stratified by major and minor depression;[129, 130] a third selected patients for persistence (based on SCL-20 scores) and then stratified by severity of depression;[131, 132] in addition, one trial presented results for the overall group.[132]

Of the two trials stratified by major and minor depression, one demonstrated statistically significant improvement in medication adherence measured by adequacy of dosage or percentage adherence for the intervention arm compared with usual care for both subgroups of major and minor depression at 7 months after randomization.[129] The other trial found improved medication adherence in the intervention arm compared with the control arm at 4 and 7 months after randomization for both major and minor depression patients for percentage adherent; with the exception of the 7-month followup for major depression, these differences were statistically significant at $p<0.05$.[130] The trial did not demonstrate significant difference for measures of adequacy of prescription for either major or minor depressive groups.

One of these trials continued to record medication adherence outcomes for 6- month intervals through 30 months after randomization;[131, 132] it reported overall differences by intervention arms at 3 and 6 months after randomization.[131, 132] Among patients severely depressed at baseline, the

intervention arm continued to show benefits of the intervention on medication adherence at 12 months.[131, 132] This effect did not extend to patients with moderate depression at 12 months, and neither group (moderate or severe depression) showed statistically significant differences between arms from 18 months onward.

These three trials suggest moderate benefit from collaborative care interventions overall (Table 61).

Other Outcomes

All three collaborative care interventions that showed a difference between arms for medication adherence also reported on changes in depression symptoms: two demonstrated statistically significant improvements in symptoms using the SCL-20 scale in the group with major depression but not in the group with minor depression.[129, 130] A third trial, with stratified results for moderate and severe depression, found statistically significant differences at 6 months following randomization in the intervention arm compared with usual care for patients with moderate depression but not for those with severe depression.[131, 132] Table 61 provides strength-of-evidence grades for this limited body of trials that suggest benefit from collaborative care.

Two of these trials reported improvement in patients' viewing antidepressant therapy as helping somewhat to a great deal (Table 55).[129, 130] Three trials reported on healthcare utilization and found conflicting but nonsignficant differences between arms (Table 56), suggesting insufficient strength of evidence (Table 61).[129-132] One trial examined costs and found no difference between study arms, and was rated insufficient (Table 57 and Table 61).[131, 132] All three trials found moderate strength of evidence of greater patient satisfaction with quality of care in the intervention arm compared with usual care (Table 58 and Table 61);[129-132] this difference was not statistically significant for the patient group with minor depression in one trial.[129]

Detailed Synthesis of Reminders to Nonadherent Patients and Lists of Nonadherent Patients to Providers

Medication Adherence

A single large trial, with a 6-month intervention, provided evidence on the utility of employing information systems as a trigger to send letters to nonadherent patients and their providers about the importance of medication adherence.[134] Patients in the intervention arm had significantly higher medication adherence at 3 and 6 months compared with those in the control arm of usual care (Table 52). Depending on the measure used (10 gap days or medication possession ratio) and the time span for the outcome (1 month, 90 days, 180 days), the difference between the arms ranged from 1 percent to 3 percent. The strength of evidence is low for effectiveness of altering information systems in improving medication adherence (Table 62).

Other Outcomes

The study notes the unknown clinical significance of such a difference in adherence rates but offers no additional data to evaluate the effect of the intervention on health outcomes.

Table 51. Depression: trial characteristics

Author, Year N at Randomization	Population Setting	Intervention and Comparator
Bogner et al., 2008[97] N=64	Patients ≥50 years Community-based primary care clinic	G1: Integrated care of depression and hypertension; care managers provided education, self-management instruction, symptom and side-effects monitoring, referral assistance G2: Usual care
Bogner et al., 2010[84] N=58	Adults ≥50 years old with diabetes mellitus and depression Community-based primary care clinic	G1: Integrated care of depression and diabetes; care managers provided education, self-management instruction, symptom and side-effects monitoring, referral assistance G2: Usual care
Capoccia et al., 2004[128] N=74	Patients ≥18 years Primary care clinics	G1: Pharmacist or pharmacy residents collaborated with primary care providers and psychiatrists; telephoned patients to address symptom and medication concerns, authorized medication refills, managed patient assistance programs, facilitated referrals, provided additional pharmacotherapy as needed; patients contacted weekly for the first month, twice a month through 3 months, every other month through 12 months G2: Usual care: patients encouraged to use available resources (clinical pharmacist, nurses, mental health professionals, primary care provider) as suggested by their primary care provider
Hoffman et al., 2003[134] N=9,564 Patients; 7,021 Providers	Patients ≥18 years and their providers Pharmacies	G1: Monthly mail-based letters sent to providers listing patients who were prescribed antidepressants and found nonadherent through pharmacy claims; letters sent to nonadherent patients with general information about medication adherence G2: Usual care
Katon et al., 1995[129] N=217	Patients ages 18-80 Primary care clinics	G1: Patients received education on depression, antidepressants, and CBT management techniques; completed a doctor-patient questionnaire to give primary care provider (PCP) and had two psychiatric visits; psychiatrists collaborated with PCP about regimens and adherence; PCPs received education on depression; case consultations, and case conferences G2: Usual care: patients received treatment for depression from PCP; could refer to mental health specialist
Katon et al., 1996[130] N=153	Patients ages 18-80 Primary care clinic	G1: Multifaceted collaborative care intervention targeting the patient, PCP, and process of care. Included behavioral treatment to manage depression and counseling to improve adherence. Patients received education on depression, antidepressants, and depression management techniques G2: Usual care: two to three visits to PCP in first 6 months following antidepressant prescription; referral to mental health services as needed.
Katon et al., 1999;[132] Katon et al., 2002[131] N=228	Patients ≥18 years Primary care providers Primary care clinics	G1: Multifaceted stepped intervention for depression persistence; Patients received education, two scheduled visits with psychiatrist, additional visits as needed, brief telephone calls; psychiatrists helped PCPs adjust dosages and medication; PCPs received immediate updates about patient progress G2: Usual care: two to four visits in first 6 months following antidepressant prescription; referral to mental health services as needed.

Table 51. Depression: trial characteristics (continued)

Author, Year N at Randomization	Population Setting	Intervention and Comparator
Katon et al., 2001;[125] Ludman et al., 2003;[126] Von Korff et al. 2003[127] N=386	Patients ages 18-80 Primary care clinics	G1: Depression relapse prevention program including education, symptom monitoring, motivational enhancement, self-management and self-care instruction, and referral facilitation in two face-to-face counseling visits, three phone calls, four personalized mailings G2: Usual care: two to four visits in first 6 months following antidepressant prescription; referral to mental health services as needed.
Lin et al., 2006[83] N=329	Adults with diabetes mellitus and persistent depression Nine primary care clinics	G1: Collaborative care: nurses worked with teams of psychiatrists and primary care providers to provide patients with stepped care G2: Usual care: patients advised to consult with PCPs for depression, who frequently prescribed antidepressants and/or referred the patient to specialty mental health services
Pyne et al., 2011[133] N=276	Patients with HIV and depression; HIV providers VA HIV clinics	G1: Collaborative stepped care with HIV and mental health providers; included education, self-management instruction, and monitoring of depression and substance abuse symptoms; referral assistance G2: Usual care: HIV providers received 1 hour of HIV and depression training; patients screened for depression at baseline and delivered results to HIV providers at most clinic visits
Rickles et al., 2005[123] N=63	Patients ≥18 years Pharmacies	G1: Pharmacists called patients three times to discuss adherence, treatment goals, education, symptoms, adverse effects, and other concerns; recommendations made as needed G2: Usual care: Education and monitoring typical of pharmacies
Simon et al., 2006[124] N=207	Patients ≥18 years Phone contacts	G1: Three phone contacts made to assess symptoms, adherence, side-effects, review algorithm for change in treatment, provide motivational enhancement; crisis intervention and care coordination as needed G2: Usual care

Abbreviations: G, group; N, number; PCP, primary care provider; VA, Department of Veterans Affairs;

Table 52. Depression: medication adherence

Study N Analyzed for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
Bogner et al., 2007[97] G1: 32 G2: 32	Adherent to antidepressants Dichotomous outcome of adherence (taken:prescribed) (≥80%) MEMS/Nonself-report	From baseline to 6 weeks, n (%): G1: 23 (71.9%) G2: 10 (31.3%) 95% CI, NR p=0.001
	Adherent to hypertension medications Dichotomous outcome of adherence (taken: prescribed) (≥80%) MEMS/Nonself-report	From baseline to 6 weeks, n (%): G1: 25 (78.1%) G2: 10 (31.3%) 95% CI, NR p<0.001
Bogner et al., 2010[84] G1: 29 G2: 29	Number and percentage of participants achieving >80% adherence to medication MEMS /Nonself-report	Oral hypoglycemics At 6 weeks, n (%) G1: 18 (62.1%) G2: 7 (24.1%) 95% CI, NR p=0.004
		Antidepressants At 6 weeks, n (%) G1: 18 (62.1%) G2: 3 (10.3%) 95% CI, NR p<0.001
Capoccia et al., 2004[128] G1: 41 G2: 33	Adherent to antidepressants (taken ≥25 days of previous 30 days) Questionnaire/Self-report	Percentage adherent at 3 months: G1: 85% G2: 81% 95% CI, NR p=NS Percentage adherent at 6 months: G1: 78% G2: 73% 95% CI, NR p=NS Percentage adherent at 9 months: G1: 48% G2: 67% 95% CI, NR p=NS Percentage adherent at 12 months: G1: 59% G2: 57% 95% CI, NR p=NS
Hoffman et al., 2003[134] G1: 4899 Pts. G2: 4665 Pts.	Adherent to antidepressants in initial month of therapy (<10 gap days in a 30-day period) Pharmacy claims records/Nonself-report	Percentage adherent at 1 month: G1: 58.9 % G2: 57.4 % 95% CI, NR p=0.136

Table 52. Depression: medication adherence (continued)

Study N Analyzed for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
	Percentage adherence using medication possession ratios (<10 gap days in a 30-day period) Pharmacy claims records/Nonself-report	Percentage adherent at 3 months: G1: 66.9 % G2: 66.5 % 95% CI, NR p<0.01 Percentage adherent at 6 months: G1: 52.3 % G2: 50.2 % 95% CI, NR p<0.001
	Percentage adherence using HEDIS guidelines (a total of 30 gap days in days 1-84 of treatment) Pharmacy claims records /Nonself-report	Percentage adherent at 3 months: G1: 59.6 % G2: 56.6 % 95% CI, NR p <0.01
	Percentage adherence using HEDIS guidelines (a total of 51 gap days in days 1-180 of treatment) Pharmacy claims records/Nonself-report	Percentage adherent at 6 months: G1: 31.5 % G2: 29.4 % 95% CI, NR p<0.05
	Persistency (defined as time span a patient continued taking antidepressants during the study). Patient considered persistent if the date of the last prescription filled plus the days supply was ≤10 days from the end of the study Pharmacy claims records /Nonself-report	Mean percentage at 2 months: G1: 45.9 % G2: 44.3 % Mean percentage at 3 months: G1: 36.8 % G2: 35.3 % Mean percentage at 4 months: G1: 30.2 % G2: 28.9 % Mean percentage at 5 months: G1: 28.8 % G2: 27.3 % Mean percentage at 6 months: G1: 24.9 % G2: 23.4 % 95%CIs and p-values: NR Mean percentage (SD) from 1-90 days: G1: 36.8 %(24.3) G2: 35.3 %(12.4) Chi-square (1 df): 0.127 95% CI, NR p:NR Mean percentage (SD) from 1-180 days: G1: 24.9 %(51.9) G2: 23.3 %(51.9) Chi-square (1 df): 0.067 95% CI, NR p:NR

Table 52. Depression: medication adherence (continued)

Study N Analyzed for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
Katon et al., 1995[129] Major depression: 91 G1: 49 G2: 42 Minor depression: 126 G1: 59 G2: 67	Patients receiving adequate dosage of antidepressants in continuation phase (3-7 months) for ≥30 days Pharmacy refill data/Nonself-report	Percentage from 3-7 months: Major depression group G1: 87.8 % G2: 57.1 % 95% CI, NR p<0.001 Minor depression group G1: 88.1 % G2: 47.8 % 95% CI, NR p<0.001
	Patients receiving adequate dosage of antidepressants in continuation phase (3-7 months) for ≥90 days Pharmacy refill data/Nonself-report	Percentage from 3-7 months: Major depression group G1: 75.5 % G2: 50.0 % 95% CI, NR p<0.01 Minor depression group G1: 79.7 % G2: 40.3 % 95% CI, NR p<0.001
Katon et al., 1996[130] Overall G1: 77 G2: 76 Major depression: 65 G1: 31 G2: 34 Minor depression: 88 G1: 46 G2: 42	Patients receiving adequate dosage of antidepressant medication for ≥30 days (AHCPR guidelines); timeframe unspecified Pharmacy refill data/Non self-report	Major depression: G1: 66.7% G2: 57.6% 95% CI, NR p<0.46 Minor depression: G1: 84.8% G2: 53.9% 95% CI, NR p<0.002
	Patients receiving adequate dosage of antidepressant medication for ≥90 days (AHCPR guidelines); timeframe unspecified Pharmacy refill data/Nonself-report	Major depression: G1: 62.1% G2: 54.6% 95% CI, NR p=0.55 Minor depression: G1: 69.6% G2: 39.5% p=0.08
	Adherent to antidepressants (taken ≥25 days of previous 30 days) Questionnaire/self-report	Percentage adherent at 1 month: Major depression: G1: 85% G2: 63% 95% CI, NR p=0.06 Minor depression: G1: 81% G2: 67% 95% CI, NR p=0.13

Table 52. Depression: medication adherence (continued)

Study N Analyzed for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
		Percentage adherent at 4 months: Major depression: G1: 89% G2: 62% 95% CI, NR p=0.02 Minor depression: G1: 74% G2: 44% 95% CI, NR p=0.01 Percentage adherent at 7 months: Major depression: G1: 79% G2: 54% 95% CI, NR p=0.07 Minor depression: G1: 64% G2: 41% 95% CI, NR p=0.04
Katon et al., 1999;[132] Katon et al., 2002[131] G1: 114 G2: 114	Patients receiving adequate dosage of antidepressants for ≥ 90 days in previous 6 months (AHCPR guidelines) Pharmacy refill data/Non elf-report	Percentage: G1: 68.8% G2: 43.8% 95% CI, NR Chi-square (1 df): 12.60 p=0.0001
	Patients receiving twice the dosage of the lower-range AHCPR guideline of antidepressant; timeframe NR Pharmacy refill data/Nonself-report	Percentage: G1: 46.8% G2: 25.7% 95% CI, NR Chi-square (1 df): 9.36 p=0.002
	Adherent to antidepressants (taken ≥25 days of previous 30 days) Questionnaire/self-report	Percentage adherent at 1 month: G1: 77.4% G2: 69.2% 95% CI, NR Chi-square (1 df): 1.38 p=0.24 Percentage adherent at 3 months: G1: 78.6% G2: 62.1 % 95% CI, NR Chi-square (1 df): 5.52 p=0.02 Percentage adherent at 6 months: G1: 73.2% G2: 50.5% 95% CI, NR Chi-square: 9.53 p=0.002

Table 52. Depression: medication adherence (continued)

Study N Analyzed for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
Among patients with moderate depression (defined as SCL-20 score ≤2.0 at baseline) N=149	Patients receiving adequate dosage of antidepressants for at least 90 days out of previous 6 months Pharmacy refill data/Nonself-report	Number (percentage) at 6 months: G1: 76% G2: 46% Chi-square (1 df)= 6.10 95% CI, NR p<0.05 At 12, 18, 24, 30 months: No significant differences across groups.
Among patients with severe depression (defined as SCL-20 score >2.0 at baseline) N=79	Adherent to adequate dosage of antidepressants for at least 90 days out of previous 6 months Pharmacy refill data/Nonself-report	Number (percentage) at 6 months: G1: 24 (72%) G2: 14 (40%) Chi-square (1 df)=8.23 95% CI, NR p<0.01 Number (percentage) at 12 months: G1: 23 (70%) G2: 13 (37%) Chi-square (1 df)=5.98 95% CI, NR p<0.05 At 18, 24, and 30 months: No significant difference across groups
Katon et al., 2001;[125] Ludman et al., 2003;[126] Von Korff et al., 2003[127] G1: 170 G2: 145	Patients who filled antidepressant prescriptions Pharmacy refill data/Nonself-report	Percentage (95%CI) from 0-3 months: G1: 80.7 % (75.1 to 86.3) G2: 65.6 % (58.8 to 72.4) Percentage (95%CI) from3-6 months: G1: 71.9 % (65.5 to 78.2) G2: 58.2% (51.2 to 65.2) Percentage (95%CI) from 6-9 months: G1: 68.4% (61.8 to 75.0) G2: 55.6% (48.5 to 62.7) Percentage (95%CI) from 9-12 months: G1: 63.2% (53.3 to 70.0) G2: 49.7% (42.6 to 56.9) Adjusted odds ratio (95%CI) across 12 months: 1.91 (1.37 to 2.65) p<0.001
	Adequate dosage of antidepressant medication Pharmacy refill data/Nonself-report	Adjusted odds ratio (95%CI) across 12 months: 2.08 (1.41 to 3.06) p<0.001
Lin et al., 2006[83] G1: 164 G2: 165	Percentage of days nonadherent to oral hypoglycemic agents at 12 Months Pharmacy refill data/Nonself-report	Mean (SD) at 12 months: G1: 28.2% (28.9%) G2: 24.0% (24.7%) 95% CI, NR p<0.03

Table 52. Depression: medication adherence (continued)

Study N Analyzed for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
	Percentage of Days Non-Adherent to lipid-lowering agents at 12 Months Pharmacy refill data/Nonself-report	Mean (SD) at 12 months: G1: 28.8% (27.1%) G2: 27.7% (24.0%) 95% CI, NR p=NS
	Adjusted mean difference in percentage of days nonadherent from baseline to 12 months Pharmacy refill data/Nonself-report	Oral hypoglycemic agent (%)=-6.3% 95% CI, -11.91 to -0.71 p=NS ACE inhibitor 6(%)=-2.5% 95% CI, -8.69 to 3.70 p=NS Lipid-lowering agent (%)=-0.2 95% CI, -7.23 to 6.76 p=NS
Pyne et al., 2011[133] G1: 123 G2: 126	Adherent to antidepressants Dichotomous outcome of adherence (taken:prescribed) over previous 4 days (≥80%) Questionnaire/self-report	At 6 months: G1: 52/66 (78.8%) G2: 50/72 (69.4%) Odds ratio (95%CI): Unadjusted: 1.60 (0.74 to 3.45) Adjusted: 1.65 (0.75 to 3.62) Adjusted p=0.22 At 12 months: G1: 45/59 (76.3%) G2: 51/60 (85.0%) Odds ratio (95%CI): Unadjusted: 0.55 (0.21 to 1.44) Adjusted: 0.56 (0.20 to 1.57) Adjusted p=0.27
	Adherent to HIV medications Dichotomous outcome of adherence (taken: prescribed) over previous 4 days (≥95%) Questionnaire/self-report	At 6 months: G1: 74/96 (77.1%) G2: 72/98 (73.5%) Odds ratio (95%CI): Unadjusted: 1.23 (0.63 to 2.40) Adjusted: 1.20 (0.60 to 2.31) Adjusted p=0.65 At 12 months: G1: 68/92 (73.9%) G2: 64/86 (74.4%) Odds ratio (95%CI): Unadjusted: 0.93 (0.46 to 1.90) Adjusted: 1.60 (0.50 to 2.33) Adjusted p=0.89

Table 52. Depression: medication adherence (continued)

Study N Analyzed for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
Rickles et al., 2005[123] G1: 28 G2: 32	Antidepressant doses omitted over previous 3 months Pharmacy refill data/Nonself-report	Number (Mean ± SD) at 3 months: G1:28 (18.1±23.5) G2: 32 (18.7±22.1) 95% CI, NR p=NS Number (Mean ± SD) at 6 months: Without ITT: G1:28 (30.3±36.4) G2: 32 (48.6±39.2) 95% CI, NR p <0.05 (one tailed) With ITT: (data NR) p=NS
Simon et al., 2006[124] G1: 98 G2: 97	Filled prescriptions for at least 90 days over 6 months of continuous antidepressant treatment Pharmacy refill data/Nonself-report	At 6 months: G1: 63 (64%) G2: 53 (55%) 95% CI, NR Chi-square (1 df): 1.88 p=0.17

Abbreviations: ACE, angiotensin-converting enzyme; AHCPR, Agency for Health Care Policy and Research; CI, confidence interval; df, degrees of freedom; HEDIS, Healthcare Effectiveness Data and Information Set; G, group; ITT, intention to treat; N, number; NR, not reported; NS, not statistically significant; RCT, randomized controlled trial; SD, standard deviation.

Table 53. Biomarkers

Author, Year N in Each Group	Outcome Source	Results
Bogner et al., 2010[84] G1: 29 G2: 29	Percentage A1C (blood glycemic control) HbA1c assays	Mean (SD) at 12 weeks: G1: 6.7 (2.3) G2: 7.9 (2.6) 95% CI, NR p=0.019

Abbreviations: HbA1C,glycosylated hemoglobin; CI, confidence interval; G, group; N, number; NR, not reported; NS, not statistically significant.

Table 54. Depression: morbidity

Author, Year N in Each Group	Outcome Source	Results
Bogner et al., 2007[97] G1: 32 G2: 32	Depression severity Center for Epidemiologic Studies-Depression Scale	Mean (SD) score at 6 weeks G1: 9.9 (10.7) G2: 19.3 (15.2) 95%CI, NR p=0.006
	Systolic blood pressure (mm Hg) Automated BP monitor	Mean (SD) at 6 weeks: G1: 127.3 (17.7) G2: 141.3 (18.8) 95% CI, NR p=0.003
Bogner et al., 2010[84] G1: 29 G2: 29	Depression severity Center for Epidemiologic Studies-Depression Scale	Mean (SD) score at 12 weeks: G1: 9.6 (9.4) G2: 16.6 (14.5) 95% CI, NR p=0.035
Katon et al., 1995[129] Major depression: 91 G1: 49 G2: 42 Minor depression: 126 G1: 59 G2: 67	Patients responding to treatment (SCL-20 score improved ≥50%)	Percentage at 4 months: Bivariate analysis: Major depression group G1: 74.4 % G2: 43.8 % 95% CI, NR p<0.01 Minor depression group G1: 60.0 % G2: 67.9 % 95% CI, NR p=0.40 Multivariate analysis: Major depression group p<0.005 Minor depression group p=NS Group-by-time interaction Major depression group p<0.004
	Patients improved Inventory of Depressive Symptomotology (IDS) score ≥50%	Percentage at 4 months: Bivariate analysis: Major depression group G1: 61.5 % G2: 40.6 % 95% CI, NR p<0.08 Minor depression group G1: 48.0 % G2: 55.4 % 95% CI, NR p=0.50 Multivariate analysis Major depression group p<0.02 Minor depression group p=NS

Table 54. Depression: morbidity (continued)

Author, Year N in Each Group	Outcome Source	Results
		Group-by-time Major depression group p: NR, but statistically significant
Katon et al., 1996[130] Overall G1: 77 G2: 76 Major depression: 65 G1: 31 G2: 34 Minor depression: 88 G1: 46 G2: 42	Patients meeting criteria for depression at 4 months DSM-III-R	Major depression group: Percentage meeting criteria for major depression: G1: 7.4% G2: 23.1% 95% CI, NR p: NR Percentage meeting criteria for minor depression: G1: 33.8% G2: 30.8% 95% CI, NR p: NR Minor depression group: Percentage meeting criteria for minor depression: G1: 25.6% G2: 33.3% 95% CI, NR p: NR
	Patients responding to treatment at 4 months (SCL-20 score improved ≥50%)	Major depression group—Percentage: G1: 70.4% G2: 42.3% 95% CI, NR p=0.04 Minor depression group—Percentage: G1: 66.7% G2: 52.8% 95% CI, NR p=0.22
Katon et al., 1999;[132] Katon et al. 2002[131] G1: 114 G2: 114	Depression severity SCL-20 depression score [0-4 range]	Rate of change in score at 3 months: 95% CI, NR F(1,186): 12.38 p=0.001 Rate of change in score at 6 months: 95% CI, NR F(1,185): 3.09 p=0.08
	Depression severity among patients with moderate depression (defined as SCL-20 score ≤ 2.0 at baseline) SCL-20 depression score [0-4 range] N=149	Adjusted mean (SD) over 28 months: G1: 1.23 (0.62) G2: 0.88 (0.52) F(1, 187): 8.65 95% CI, NR p=0.004
	Depression severity among patients with severe depression (defined as SCL-20 score > 2.0 at baseline) SCL-20 depression score [0-4 range] N=79	Adjusted mean, (SD) over 28 months: G1: 1.16, (0.85) G2: 1.19, (0.72) F(1.51): 0.02 95% CI, NR p=0.88

Table 54. Depression: morbidity (continued)

Author, Year N in Each Group	Outcome Source	Results
	Asymptomatic patients DSM-IV score of 0 or 1	Percentage at 3 months G1: 40% G2: 23% 95% CI, NR Chi-square (1 df): 6.18 p=0.01 Percentage at 6 months G1: 44% G2: 31% 95% CI, NR Chi-square (1 df): 3.90 p=0.05
	Functional impairment, Disability, among patients with moderate depression (defined as SCL-20 score ≤ 2.0 at baseline) Sheehan Disability Scale	Adjusted mean (SD) over 28 months: G1: 3.09 (2.30) G2: 3.58 (2.37) F(1.87): 1.21 95% CI, NR p=0.27
	Functional impairment, Disability, among patients with severe depression (defined as SCL-20 score > 2.0 at baseline) Sheehan Disability Scale	Adjusted mean (SD) over 28 months: G1: 3.41 (2.61) G2: 3.20 (2.66) F (1.51): 0.09 95% CI, NR p=0.76
Katon et al., 2001;[125] Ludman et al., 2003;[126] Von Korff et al., 2003[127] G1: 170 G2: 145	Depression severity among patients with severe depression (defined as SCL-20 score >2.0 at baseline) N=79	Mean difference in scores between groups across 12 months: 0.08 p=0.04 Mean (SD) score at 3 months G1: 0.75 (0.55) G2: 0.79 (0.47) 95% CI, NR p: NR *Sig difference between 2 depression specialists Mean (SD) score at 6 months G1: 0.74 (0.54) G2: 0.78 (0.51) 95% CI, NR p: NR Mean (SD) score at 9 months G1: 0.69 (0.56) G2: 0.86 (0.57) 95% CI, NR p: NR Mean (SD) score at 12 months G1: 0.65 (0.51) G2: 0.74 (0.54) 95% CI, NR p: NR

Table 54. Depression: morbidity (continued)

Author, Year N in Each Group	Outcome Source	Results
	Functional impairment, Disability Sheehan Disability Scale	Mean score (SD) at 3 months G1: 2.79 (3.94) G2: 2.08 (2.07) 95% CI, NR p: NR Mean score (SD) at 6 months G1: 2.41 (3.23) G2: 2.23 (2.22) 95% CI, NR p: NR Mean score (SD) at 9 months G1: 2.30 (2.06) G2: 2.30 (2.28) 95% CI, NR p: NR Mean score (SD) at 12 months G1: 2.09 (1.98) G2: 2.08 (2.07) 95% CI, NR p: NR Intervention effect (SD): Estimate: 0.15 (0.17) T-statistic: 0.86 p=0.39 Time effects (SD) Estimate: -0.06 (0.06) T-statistic: 1.06 p=0.29 Intervention x time effects (SD) Estimate: -0.12 (0.08) T-statistic: 1.47 p=0.14
	Functional impairment, SF-36 Social Functioning scale, using imputed data and adjusting for baseline characteristics	Mean score (SD) at 3 months G1: 81.4 (20.5) G2: 81.1 (21.1) 95% CI, NR p: NR Mean score (SD) at 6 months G1: 83.3 (20.2) G2: 83.0 (20.9) 95% CI, NR p: NR Mean score (SD) at 9 months G1: 84.7 (19.7) G2: 81.4 (22.4) 95% CI, NR p: NR

Table 54. Depression: morbidity (continued)

Author, Year N in Each Group	Outcome Source	Results
		Mean score (SD) at 12 months G1: 86.9 (17.8) G2: 81.7 (20.4) 95% CI, NR p: NR Intervention effects (SD): Estimate: 0.27 (1.42) T-statistic: 0.19 p=0.85 Time effects (SD) Estimate: 0.66 (0.48) T-statistic: 1.38 p=0.17 Intervention x time effects (SD) Estimate: 1.31 (0.66) T-statistic: 1.98 p=0.047
	Functional impairment, SF-36 Role-Emotional scale, using imputed data and adjusting for baseline characteristics	Mean score (SD) at 3 months G1: 67.2 (35.6) G2: 68.3 (35.6) 95% CI, NR p: NR Mean score (SD) at 6 months G1: 67.8 (36.5) G2: 72.1 (31.8) 95% CI, NR p: NR Mean score (SD) at 9 months G1: 70.8 (36.3) G2: 71.0 (34.3) 95% CI, NR p: NR Mean score (SD) at 12 months G1: 75.9 (32.2) G2: 73.9 (36.2) 95% CI, NR p: NR Intervention effects (SD): Estimate: -1.52 (2.21) T-statistic: 0.69 p=0.49 Time effects (SD) Estimate: 2.51 (0.88) T-statistic: 2.86 p=0.004

Table 54. Depression: morbidity (continued)

Author, Year N in Each Group	Outcome Source	Results
		Intervention x time effects (SD) Estimate: 0.32 (1.16) T-statistic: 0.28 p=0.78

Abbreviations: CI, confidence interval; df, degree of confidence; G, group; IDS, Inventory of Depressive Symptomatology; ITT, intention to treat; N, number; NR, not reported; NS, not statistically significant; SCL-20, Hopkins Symptom Checklist-20;SD, standard deviation.

Table 55. Patient satisfaction

Author, Year N in Each Group	Outcome Source	Results
Katon et al., 1995[129] Major depression: 91 G1: 49 G2: 42 Minor depression: 126 G1: 59 G2: 67	Patients reporting antidepressant medications as helping somewhat to a great deal Questionnaire with 4-point ordinal scale	Percentage at 4 months: Major depression group G1: 88.1 % G2: 63.3 % 95% CI, NR p<0.01 Minor depression group G1: 81.8 % G2: 61.4 % 95% CI, NR p<0.02
Katon et al. 1996[130] Overall G1: 77 G2: 76 Major depression: 65 G1: 31; G2: 34 Minor depression: 88 G1: 46; G2: 42	Patients rating antidepressant medication as helping somewhat to a great deal Questionnaire with 4-point ordinal scale	Percentage, at 4 months: Major depression group G1: 80% G2: 58.3% 95% CI, NR p<0.10 Minor depression group G1: 94.6% G2: 88.6% 95% CI, NR p=0.36

Abbreviations: CI, confidence interval; G, group; N, number; NR, not reported; NS, not statistically significant; SD, standard deviation.

Table 56. Healthcare utilization

Author, Year N in Each Group	Outcome Source	Results
Katon et al.,1995[129] Major depression: 91 G1: 49 G2: 42 Minor depression: 126 G1: 59 G2: 67	Number of study visits for collaborative care intervention (G1 only: N: 108) Medical records	Mean (SD) at 12 months: 3.9 (2.5)
	Number of visits with primary care provider for depression (not study-related) Medical records	Mean (SD) at 12 months: G1: 4.5 (3.7) G2: 3.7 (2.4) 95% CI, NR p: NR
	Patients seen by a mental health specialist (not study-related) Medical records	Number (%) at 12 months: G1: 30 (27%) G2: 34 (31%) 95% CI, NR p: NR
	Patients seen by a psychiatrist (not study-related) Medical records	Number (%) at 12 months: G1: 3 (3%) G2: 11 (10%) 95% CI, NR p: NR
Katon et al., 1996[130] Overall G1: 77 G2: 76	Number of visits with primary care provider Medical records	Within first 12 weeks of treatment: Mean (SD) G1: 3.1 (1.7) G2: 2.9 (1.4) 95% CI, NR p=0.30 Within first 6 months after primary care referral visit: Mean (SD) G1: 4.6 (2.6) G2: 4.1 (2) 95% CI, NR p=0.19
	Patients seen by a mental health specialist Medical records	Within first 12 weeks of treatment: Percentage: G1: 20% G2: 29% 95% CI, NR p=0.21 Within first 6 months after primary care referral visit: G1: 24% G2: 33% 95% CI, NR p=0.21

Table 56. Healthcare utilization (continuation)

Author, Year N in Each Group	Outcome Source	Results
Katon et al., 1999;[132] Katon et al., 2002[131] G1: 114 G2: 114	Number of visits with primary care provider Data source unspecified	Mean (SD) at 3 months: G1: 1.6 (1.8) G2: 1.8 (1.8) 95% CI, NR Chi-square (1 df): 1.46 p=0.23 Mean (SD) at 6 months: G1: 3.4 (4.3) G2: 3.3 (3.1) 95% CI, NR Chi-square (1 df): 0.35 p=0.55
	Patients with ≥1 visit to a nonstudy mental health specialist Data source unspecified	Percentage at 3 months: G1: 17.5% G2: 24.6% 95% CI, NR Chi-square (1 df): 1.29 p=0.26 Percentage at 6 months: G1: 24.6% G2:27.2% 95% CI, NR Chi-square (1 df): 0.09 p=0.76
	Number of visits to a nonstudy mental health specialist Data source unspecified	Mean (SD) at 3 months: G1: 0.6 (1.7) G2: 0.8 (1.9) 95% CI, NR p=0.34 Mean (SD) at 6 months: G1: 1.3 (2.9) G2: 1.3 (2.9) 95% CI, NR p=0.85

Abbreviations: CI, confidence interval; df, degrees of freedom; G, group; N, number; NR, not reported; NS, not statistically significant; SD, standard deviation.

Table 57. Costs

Author, Year N in Each Group	Outcome Source	Results
Katon et al., 1999;[132] Katon et al., 2002[131] G1: 114 G2: 114	Total ambulatory costs Health plan computerized data	Mean (95%CI) over 36 months: G1: $8,524 (5,059-8,188) G2: $7,787 (6,595-8,980) F(1,180): 0.77 p=0.40
	Total health care costs Health plan computerized data	Mean (95%CI) over 36 months: G1: $9,799 (7,763-11,834) G2: 9,192 (7,504-10,880) F(1,180): 0.91 p=0.34
	Depression treatment costs Health plan computerized data	Over 36 months: F(1,173): 2.65 p=0.10
	Nondepression related outpatient costs Health plan computerized data	Mean (95%CI) over 36 months: G1: $6,769 (5,351-8,188) G2: $5,470 (4,431-6,510) F(1,180): 0.11 p=0.74

Abbreviations: CI, confidence interval; F, Fisher-Snedecor distribution; G, group; N, number; NR, not reported.

Table 58. Quality of care

Author, Year N in Each Group	Outcome	Results
Katon et al., 1995[129] Major depression: 91 G1: 49 G2: 42 Minor depression: 126 G1: 59 G2: 67	Patients rating quality of depression care as good to excellent on a 5-point scale from poor to excellent	Percentage at 4 months: Major depression group G1: 93.0 % G2: 75.0 % 95% CI, NR p<0.03 Minor depression group G1: 94.4 % G2: 89.3 % 95% CI, NR p=0.30
Katon et al., 1996[130] Overall G1: 77 G2: 76 Major depression: 65 G1: 31; G2: 34 Minor depression: 88 G1: 46; G2: 42	Patients rating quality of depression care as good to excellent on a 5-point scale from poor to excellent	Percentage at 4 months: Major depression group G1: 88.5% G2: 56% 95% CI, NR p<0.009 Minor depression group G1: 97.1% G2: 71.4% 95% CI, NR p=0.003
Katon et al., 1999;[132] Katon et al., 2002[131] G1: 114 G2: 114	Patients rating the quality of care received for depression as good to excellent on a 5-point scale from poor to excellent	Percentage at 3 months: G1: 94.5% G2: 63.9% 95% CI, NR Chi-square (1 df): 23.51 p<0.00001 Percentage at 6 months: G1: 79.5% G2: 63.5% 95% CI, NR Chi-square (1 df): 4.21 p=0.04

Abbreviations: CI, confidence interval; df, degrees of freedom; G, group; N, number; NR, not reported.

Table 59. Depression: strength of evidence for telemonitoring or telephone care interventions

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Telemonitoring or telephone care vs. usual care	2; 270 (255)	Medication Adherence	RCT Medium	Inconsistent	Direct	Imprecise	Insufficient
	0	Mortality	NA	NA	NA	NA	Insufficient
	0	Biomarkers	NA	NA	NA	NA	Insufficient
	0	Symptom improvement	NA	NA	NA	NA	Insufficient
	0	Quality of care	NA	NA	NA	NA	Insufficient
	0	Patient satisfaction	NA	NA	NA	NA	Insufficient
	0	Quality of life	NA	NA	NA	NA	Insufficient
	0	Healthcare utilization	NA	NA	NA	NA	Insufficient

Abbreviations: NA not applicable; RCT, randomized controlled trial.

Table 60. Depression: strength of evidence for case management interventions

Intervention	Number of Trials; Subjects (Analyzed)	Outcome	Study Design/Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Case management vs. usual care	3; 508 (437)	Medication adherence	RCT Medium	Consistent	Direct	Precise	Difference in percentage points for adherence or filling prescriptions over time: 9-15 (range across studies) Moderate SOE of benefit
	0	Mortality	NA	NA	NA	NA	Insufficient
	1; 64 (64)	Diastolic and systolic blood pressure	RCT Low	Unknown	Direct	Precise	Difference in systolic: 14.0 mm Hg; Difference in diastolic: 9.2 mmHG Low SOE of benefit
	1; 64 (64)	HbA1c	RCT Low	Unknown	Direct	Precise	Difference in HbA1C: 1.2 Low SOE of benefit
	3; 508 (437)	Symptom improvement	RCT Medium	Consistent	Direct	Precise	Difference in CES-D scale: 7.0-9.4 (range across studies) Mean difference in SCL-20 (0-4 range) scores between groups across 12 months: 0.08 Moderate evidence of benefit
	1; 386 (315)	Self-reported disability	RCT Medium	Unknown	Indirect	Imprecise	Varied outcomes, time periods, and consistency Insufficient
	0	Quality of care	NA	NA	NA	NA	Insufficient
	0	Patient satisfaction	NA	NA	NA	NA	Insufficient
	0	Quality of life	NA	NA	NA	NA	Insufficient
	0	Healthcare utilization	NA	NA	NA	NA	Insufficient

Abbreviations: HbA1C, hemoglobin A1C; CES-D scale, Center for Epidemiologic Studies-Depression scale; NA not applicable; RCT, randomized controlled trials; SCL-20, Hopkins Symptom Checklist-20; SOE, strength of evidence.

Table 61. Depression: strength of evidence for collaborative care interventions

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Study Design/ Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Collaborative care vs. usual care	3 (telephone and in-person); 598 (598)	Medication adherence	RCT Medium	Consistent	Direct	Precise	Difference in percentage points for adherence: 16.5 to 40.3 (range across studies) Moderate SOE
	1 (telephone only); 74 (74)	Medication adherence	RCT Medium	Unknown	Direct	Imprecise	Difference in percentage points for adherence: -19 to 2 (range across studies) Insufficient
	2; 605 (578) Depression and HIV ; Depression and diabetes	Medication adherence	RCT Medium	Inconsistent	Direct	Imprecise	Difference in percentage points for adherence: -8.7 to 9.4 (range) Insufficient for patients with depression and another chronic disease
	0	Mortality	NA	NA	NA	NA	Insufficient
	0	Biomarkers	NA	NA	NA	NA	Insufficient
	2; 156 (156) Major depression	Symptom improvement	RCT Medium	Consistent	Direct	Imprecise	Varied magnitude based on outcome and time periods Low SOE
	2; 214 (214) Minor depression	Symptom improvement	RCT Medium	Inconsistent	Direct	Imprecise	Varied magnitude based on outcome and time periods Insufficient
	1; 149 (149) Moderate depression	Symptom improvement	RCT Medium	Unknown	Direct	Precise	Varied magnitude based on outcome and time periods Low SOE
	1; 79 (79) Severe depression	Symptom improvement	RCT Medium	Unknown	Direct	Imprecise	Varied magnitude based on outcome and time periods Insufficient for severe depression
	2; 370 (370)	Patient satisfaction with utility of antidepressants	RCT Medium	Consistent	Direct	Imprecise	Difference in percentage points in those rating antidepressants as helping somewhat to a great deal: 6.0-24.7 (range across studies) at 4 months Low SOE
	0	Quality of life	NA	NA	NA	NA	Insufficient
	3; 598 (598)	Healthcare utilization	RCT Medium	Inconsistent	Direct	Imprecise	Varied outcomes, time periods, and consistency Insufficient

Table 61. Depression: strength of evidence for collaborative care interventions (continued)

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Study Design/ Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
	1; 228 (228)	Costs	RCT Medium	Unknown	Direct	Imprecise	Direction and magnitude of difference varies by type of cost Insufficient
	3; 598 (598)	Patient satisfaction with quality of care	RCT Medium	Consistent	Direct	Precise	Difference in percentage points in those rating quality of care as good to excellent: 5.1-30.6 (range across studies) at 3-4 months; 16 at 6 months Moderate SOE

Abbreviations: NA not applicable; RCT, randomized controlled trials; SOE, strength of evidence.

Table 62. Depression: strength of evidence for information systems change interventions

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Study Design/Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Information systems change vs. usual care	1; 9,564 (9,564)	Medication Adherence	RCT Medium	Consistent	Direct	Precise	Difference in percentage points for adherence; 1-3 (range across studies) Low SOE
	0	Mortality	NA	NA	NA	NA	Insufficient
	0	Biomarkers	NA	NA	NA	NA	Insufficient
	0	Symptom improvement	NA	NA	NA	NA	Insufficient
	0	Quality of care	NA	NA	NA	NA	Insufficient
	0	Patient satisfaction	NA	NA	NA	NA	Insufficient
	0	Quality of life	NA	NA	NA	NA	Insufficient
	0	Healthcare utilization	NA	NA	NA	NA	Insufficient

Abbreviations: NA not applicable; RCT, randomized controlled trials; SOE, strength of evidence.

Key Question 1. Glaucoma: Medication Adherence Interventions

Description of Included Studies

Overview

One study, rated medium for risk of bias, examined an intervention that attempted to improve medication adherence among patients with glaucoma.[135] Table 63 presents study characteristics;

Table 64 shows medication adherence results; and Table 65 presents morbidity outcomes.

Population

The study population included patients ages 18 years or older with diagnosis of open-angle glaucoma, angle-closure glaucoma, glaucoma suspect, or ocular hypertension who had been prescribed eye drops for their condition.

Intervention

This study was directed at patients. The study used a multicomponent intervention consisting of an education video, discussion of barriers and strategies, reminder phone calls, and a dosing aid.

Control

The control group received no additional intervention except for an instruction to take their eye drops as indicated.

Outcome and Timing

The study did not report on the initiation of therapy, and reported proportion of prescribed doses taken as well as changes in adherence rates. Medication adherence was measured as proportion of prescribed doses taken and changes in adherence rates (from the end of an observational cohort period and the end of the randomized controlled trial period in the study). These measurements were taken using a dosing aid that was downloaded at the appropriate times for measurement. In addition, we evaluated health outcomes because this study reported a significantly higher medication adherence in the intervention arm compared with the control arm. The study reported a health outcome of intraocular pressure for glaucoma patients measured in millimeters of Mercury (mmHg). Medication adherence outcomes were measured using downloaded dosing aids from patients, which were obtained at the end of the randomized control trial period (6 months into the overall study period, which included an initial 3-month observational study).

Setting

The study was conducted at two eye clinics.

Applicability

The applicability of this study is limited by the availability of dosing aids such as those tested in this intervention.

Key Points

Overview

- A single study provided evidence on improving medication adherence and other outcomes for glaucoma.

Multicomponent Intervention for Glaucoma

- Medication adherence: one study provided evidence of benefit for improved medication adherence (low strength of evidence)

- Morbidity (intraocular pressure): Because of lack of precision, we were unable to judge the true effect of the intervention on intraocular pressure, and rated the evidence as insufficient.
- All other outcomes: We rated all other outcomes as insufficient due to lack of evidence

Detailed Synthesis of Results

This multicomponent intervention significantly improved medication adherence, as measured with dosing aids (proportion of pills taken and change in adherence rate) (Table 64).

This study also presented specific morbidity outcomes. Intraocular pressure did not significantly improve in the between baseline to 3 months, or up to 6 months after the end of the intervention (Table 65).

Table 63. Glaucoma: study characteristics

Author, Year N at Randomization	Population Setting	Intervention and Comparator
Okeke et al., 2009[135] N=127	Adults≥18 years of age; with diagnosis of open-angle glaucoma, angle-closure glaucoma, glaucoma suspect, or ocular hypertension; who were using or prescribed a topical prostaglandin analog; who were able to return for 3- and 6-month follow-up visits; with ≤75% adherence to eye drops during phase 1 of the study (a 3-month observational cohort) Two eye clinics	G1: Educational video stressing importance of drop-taking and suggesting strategies to improve adherence, discussion of barriers and strategies with study coordinator, reminder phone calls (weekly for first month, then once every other week for next 2 months), use of a dosing aid with audible and visible alarms G2: Controls were told that it is important to take their eye drops as prescribed, but had no other intervention

Table 64. Glaucoma: medication adherence

Study N for Each Group N Analyzed	Adherence Measure Source/Method	Outcomes for Each Time Point
Okeke et al., 2009[135] G1: 35 G2: 31	Proportion of prescribed doses taken Measured with dosing aids downloaded after the observational cohort period (capturing data for a 3-month period) and at the end of the RCT (capturing data for a 3-month period)/Nonself-report	G1: adherence rate (SD) 0.73 (0.22) G2: adherence rate (SD) 0.51 (0.30) 95% CI, NR p: 0.001
G1: 35 G2: 31	Change in adherence rates (unadjusted) Measured with dosing aids downloaded after the observational cohort period (capturing data for a 3-month period) and at the end of the RCT (capturing data for a 3-month period) /Nonself-report	G1: change in adherence rate (SD) 0.19 (0.20) G2: change in adherence rate (SD) 0.06 (0.23) 95% CI, NR p: 0.01
G1: 34 G2: 28	Change in adherence rates (adjusted) Measured with dosing aids downloaded after the observational cohort period (capturing data for a 3-month period) and at the end of the RCT (capturing data for a 3-month period)/Nonself-report	G1: change in adherence rate (SD) 0.21 (0.05) G2: change in adherence rate (SD) -0.002 (0.04) 95% CI, NR p: 0.0001

Abbreviations: CI, confidence interval; G, group; NR, not reported; RCT, randomized controlled trial; SD, standard deviation

Table 65. Glaucoma: morbidity

Author, Year N in Each Group	Outcome	Results
Okeke et al., 2009[135] G1: NR G2: NR	Intraocular pressure	G1: NR, Applantoin G2: NR, Applantoin 95 % CI, NR p: 0.81

Abbreviations: CI, confidence interval; G, group; NR, not reported;

Table 66. Multicomponent intervention for glaucoma: strength of evidence

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Software-based telephone counseling	1; 66	Proportion of prescribed doses taken	RCT Medium	Unknown	Direct	Precise	Difference in adherence rate: 0.22 Low SOE of benefit
	0	Mortality	NA	NA	NA	NA	Insufficient
	0	Biomarkers	NA	NA	NA	NA	Insufficient
	1; 66	Morbidity: Intraocular pressure	NA	Unknown	Direct	Imprecise	Insufficient
	0	Patient satisfaction	NA	NA	NA	NA	Insufficient
	0	Quality of life	NA	NA	NA	NA	Insufficient
	0	Health care utilization	NA	NA	NA	NA	Insufficient
	0	Quality of care	NA	NA	NA	NA	Insufficient

N: number; NA, not applicable; NR: not reported; RCT, randomized controlled trial; SOE, strength of evidence.

Key Question 1. Multiple Sclerosis: Medication Adherence Interventions

Description of Included Studies

Overview

One study, with medium risk of bias, provided evidence on interventions to improve medication adherence among patients with multiple sclerosis (MS).[136] Table 67 presents study characteristics and Table 68 presents medication adherence results.

Population

The study population consisted of adult MS patients who were on Avonex® (interferon beta-1a) treatment for their MS.

Software-based Telephone Counseling Intervention

The intervention was directed at patients and systems. (Table 67). In this study, call center staff at the Biogen call center (Biogen Idec manufactures Avonex, the MS treatment examined in this study) used a software-based counseling intervention. This software, which was based on the transtheoretical model of change and motivational interviewing, focused on increasing persistence in therapy-taking for MS patients. The software program guided call center staff members with appropriate messages to convey to patients during telephone calls about Avonex therapy continuation. Patients in the control group did not receive telephone calls from Biogen call center staff, but were provided with a toll-free hotline number with which they could reach the call center if needed.

Outcome and Timing

The study did not report on the initiation of therapy. It presented persistence outcomes, looking specifically at discontinuation of Avonex therapy for MS. The study reported improvement in medication persistence in the intervention arm, but did not present other health outcomes.

Setting

The study was conducted with a group of MS patients who were contacted by a pharmaceutical company (Biogen).

Applicability

While the intervention itself was broadly applicable, recruitment of patients was stratified by readiness to change, which likely makes the population not representative, and hence limits applicability of findings.

Key Points

Overview

- A single study provided evidence on improving medication adherence and other outcomes for MS.

Software-based Telephone Counseling Intervention for MS

- Medication adherence: evidence of benefit (low strength of evidence)
- All other outcomes: insufficient for lack of evidence

Detailed Synthesis of Results

The intervention, based on the transtheoretical model of change, significantly improved medication persistence for individuals with MS (as measured by proportion of patients who discontinued MS treatment) when compared with those who did not receive this intervention (Table 68).

Table 67. Multiple sclerosis: study characteristics

Author, Year N at Randomization	Population Setting	Intervention and Comparator
Berger et al., 2009[136] N=435	Adults currently on MS therapy with Avonex Network of patients with MS contacted by Biogen	G1: Software-based counseling intervention where patients were contacted every 2 or every 4 weeks (depending on stage of readiness and importance of the medicine) by call center staff who used web-based software to guide them through motivational interviewing (MI)-based counseling sessions. G2: Patients did not receive calls, but had access to call center staff via standard toll-free hotline mechanisms.

Abbreviations: G, group; MS, multiple sclerosis.

Table 68. Multiple sclerosis: medication adherence

Outcome Measured	Study N for Each Group N Analyzed	Adherence Measure Source/Method	Outcomes for Each Time Point
Self-Reported Measures of Adherence	Berger et al., 2009[144] G1: 172 G2: 195	Percentage of patients who discontinued use of Avonex therapy for MS Self-report at 3 months	G1: 2 (1.2%) discontinued G2: 17 (8.7%) discontinued 95 % CI, NR p: 0.001

Abbreviations: CI, confidence interval; G, group; MS, multiple sclerosis; NR, not reported.

Table 69. Software-based telephone counseling interventions for MS: strength of evidence

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Software-based telephone counseling	1; 367	Percentage of patients who discontinued therapy	RCT Medium	Unknown	Direct	Precise	Difference in percentage points of patients who discontinued use of MS therapy: -7.5 Low SOE of benefit
	0	Mortality	NA	NA	NA	NA	Insufficient
	0	Biomarkers	NA	NA	NA	NA	Insufficient
	0	Morbidity	NA	NA	NA	NA	Insufficient
	0	Patient satisfaction	NA	NA	NA	NA	Insufficient
	0	Quality of life	NA	NA	NA	NA	Insufficient
	0	Health care utilization	NA	NA	NA	NA	Insufficient
	0	Quality of care	NA	NA	NA	NA	Insufficient

Abbreviations: N: number; NA, not applicable; NR: not reported; RCT, randomized controlled trial; SOE, strength of evidence.

Key Question 1. Musculoskeletal Diseases: Medication Adherence Interventions

Description of Included Studies

Overview

We found two studies that examined interventions designed to improve medication adherence in populations that had musculoskeletal diseases.[137, 138] We rated one study as having low risk of bias[137] and the other study as having medium risk of bias.[138] Table 70 presents study characteristics. Table 71 and Table 72 provide results for medication adherence and patient satisfaction, respectively.

Population

Specifically, one study focused on populations with rheumatoid arthritis, psoriatic arthritis, and inflammatory arthritis;[137] the other study focused on populations with osteoporosis.[138]

Intervention

Both studies were directed at patients and systems-level change.[137, 138] In one study, the intervention consisted of individualized care, which included appointments with a health educator in addition to standard rheumatology care, a notebook containing Arthritis Foundation pamphlets, medicine calendars, and a map of the hospital.[137] In the other study, the intervention group received care from a physician assistant and monthly telephone conversations with staff in a virtual osteoporosis clinic (Table 70).

Comparator

In one study, the control group received usual care, defined as referral to and evaluation and treatment from, a primary care physician.[138] In the other study, the control group received standard care, defined as care from their rheumatologist.[137]In addition, patients in the standard care group also received pamphlets from the Arthritis Foundation, examples of medicine calendars, and a map of the hospital.[137]

Outcome and Timing

One study examined initiation of treatment measured by examining the percentage of study subjects who filled osteoporosis medication within 130 days of enrolling in the study.[138] The second study examined adherence.[137] Adherence was measured using a self-report from patients and creating a mean score of adherence at various time points (baseline, 6 months, and 12 months).[137] The change in adherence from baseline to various time points was also measured.[137] In addition, for those studies in which an improvement in medication adherence was seen due to the intervention, we included relevant health outcomes when reported. Such information, specifically patient satisfaction outcomes, which was an overall self-reported level of satisfaction regarding osteoporosis treatment, was relevant and reported for one study.[138]

Setting

One study was conducted in an arthritis center of an urban teaching hospital.[137] The other study, focused on patients with osteoporosis, was conducted at the Kaiser Permanente San Diego Department of Preventive Medicine.[138]

Applicability

We found both studies to be broadly applicable due to the ease of implementation of the interventions described.[137, 138]

Key Points

- Two studies evaluated medication adherence; one of two reported improvement in medication adherence.
- Both studies were directed at patients and systems-level change.
- We evaluated other outcomes for the single study that showed improvement in medication adherence.
- Medication adherence: imprecise outcomes (insufficient strength of evidence)

- Patient satisfaction: imprecise outcomes (insufficient strength of evidence)
- All other outcomes: insufficient for lack of evidence

Detailed Synthesis for Case Management Interventions for Musculoskeletal Diseases

Medication Adherence

One study examined initiation of treatment and showed that a telephone-based virtual clinic intervention can increase the use of osteoporosis medication among newly diagnosed women (Table 71).[138]

Initiation of treatment was measured by examining the percentage of women who were using osteoporosis medication (at 1 year and 30 days from entry into the study) using a pharmacy database.

One study examined adherence but did not show a significant effect of the intervention on adherence.[137]Neither study examined persistence in adherence.

Other Outcomes

In one study where medication adherence outcomes were improved for those in the intervention group,[138] patient satisfaction outcomes were collected using a poststudy questionnaire completed by approximately 65 percent of women in both the intervention and the control groups (Table 72). However, no significant differences were seen between groups when women were asked whether their treatment experiences for osteoporosis were good.

Table 70. Musculoskeletal diseases: study characteristics

Author, Year N at Randomization	Population Setting	Intervention and Comparator
Rudd et al., 2009[137] N=127	Adults ≥18 years of age; with rheumatoid arthritis, psoriatic arthritis, and inflammatory arthritis; who had ≥1 visit with rheumatologist (the rheumatologist must have consented to helping with the study) Arthritis center in an urban teaching hospital	G1: Individualized care which included standard rheumatology care; a notebook containing Arthritis Foundation pamphlets written in plain language (5-8th grade on the SMOG readability formula), examples of medicine calendars, and a map of the hospital; and two appointments with a health educator, each after a rheumatology appointment. Originally there were two intervention groups (individualized care and plain English material), but due to slow recruitment the latter was absorbed into the former. 13 participants received only the plain English materials and are included with the individualized care arm in some analyses but excluded in others. G2: Received standard rheumatology care and a notebook containing Arthritis Foundation pamphlets (11-15th grade on SMOG), examples of medicine calendars, and a map of the hospital.
Waalen et al., 2009[138] N=235	Women ≥60 years of age, who had uncomplicated osteoporosis (per National Osteoporosis Foundation guidelines), and who had not previously identified as having osteoporosis Kaiser Permanente San Diego Department of Preventive Medicine	G1: Patients received care from a PA under the supervision of a preventive medicine physician. Patients were given prescriptions for vitamin D with or without calcium depending on their vitamin D levels. They received educational handouts in a one-time mailing. They had an open-ended phone discussion with the osteoporosis clinic about osteoporosis treatment, followed by monthly calls until the patient started taking the medication and reported no problems. They were given a 3-month prescription for a second-generation biphophonate. Patients who needed help paying for the med were assisted in obtaining the drug from the study sponsor (Merck). G2: Patients received a referral to their usual primary care physician and were told they would be contacted by the PCP for followup. All subsequent evaluation and treatment were performed by the PCP, and no further contact with the patient was initiated by the osteoporosis clinic until the end of the study.

Abbreviations: G, group; N, number; PA, physician assistant; PCP, primary care physician; SMOG: Simple Measure of Gobbledygook readability formula which indicates the educational level required to read and understand text.[145]

Table 71. Musculoskeletal diseases: medication adherence

Study N for Each Group N Analyzed	Adherence Measure Source/Method	Outcomes for Each Time Point
Rudd et al., 2009[137]	Mean score on adherence to treatments scale (0=best, 3=worst)	
G1: 51 G2: 63	Self-report at baseline,	Baseline mean (SD) G1: 0.40 (0.40) G2: 0.30 (0.37)
G1: 49 G2: 57	Self-report at 6 months	6m mean (SD) G1: 0.23 (0.28) G2: 0.24 (0.32)
G1: 48 G2: 57	Self-report at 12 months	12m mean (SD) G1: 0.17 (0.25) G2: 0.18 (0.30)
G1: 49 G2: 57	Percentage change at 6 months in medication adherence outcome Self-report at 6 months (scales show improvement with decreased scores)	Baseline to 6 months G1: -4.76 G2: 0.25 95% CI, NR p: 0.33
G1: 48 G2: 57	Percentage change at 12 months in medication adherence outcome Self-report at 12 months (scales show improvement with decreased scores)	Baseline to 12 months G1: -12.21 G2: -3.12 95% CI, NR p: 0.10
Waalen et al., 2009[138] G1: 109 G2: 102	Percentage of women using osteoporosis medication Measured at 1 year and 30 days from entry into study using pharmacy database/nonself-report	G1: 68.8% G2: 45.1% 95% CI, NR p: <0.001

Abbreviations: CI, confidence interval; G, group; m, month; NR, not reported; SD, standard deviation

Table 72. Musculoskeletal diseases: patient satisfaction

Author, Year N in Each Group	Outcome	Results
Waalen et al., 2009[138] G1: 68 G2: 58	Response to the question: "Overall my treatment for osteoporosis has been a good experience" Measured at 1 year and 30 days after study entry	Percentage of patients responding All/most of the time: G1: 85.3 G2: 89.7 Some of the time: G1: 5.9 G2: 0 A little/none of the time: G1: 8.8 G2: 10.3 Overall p: 0.17

Abbreviations: G, group.

Key Question 1. Unspecified or Multiple Chronic Conditions: Medication Adherence Interventions

Description of Included Studies

Overview

We found four studies that examined interventions designed to improve medication adherence in populations that had unspecified or multiple chronic conditions,[139-142] Of the four studies included for this portion of the review, we rated one study as having a low risk of bias,[140] and three studies as having medium risk of bias.[139, 141, 142] Table 73 presents study characteristics, Table 74 results for medication adherence, and Table 75 strength of evidence grades.

Population

We included studies that populations with various multiple or unspecified chronic conditions. In studies where the multiple conditions were specified, they included diabetes, hypertension, hyperlipidemia, and depression.

Intervention

In three of these four studies, the intervention included interaction with a pharmacist.[139, 140, 142] In the fourth study, an interdisciplinary medical and psychosocial assessment, coupled with a follow-up case management, formed the basis for what the authors termed as a "primary intensive care" intervention.[141]

Comparator

The comparator in each case was a usual-care control group; a care environment that was not affected by the intervention arm of the study and that followed what constituted a typical standard of care for that group of patients. The specific components of usual care varied considerably based on the study, since each study had a different combination of chronic diseases as well as different intervention components. In one study where the intervention consisted of an interdisciplinary care environment, usual care was care directed by the primary

care provider in which the same psychiatrist who provided consultation services for the intervention group provided consultation for control group patients, but only if the provider specifically requested it.[141] Usual care in one study was described as regular filling of prescriptions as requested by patients, without the pharmacist contact that the intervention included.[139] In another study examining interventions that included pharmacist contact, usual care included routine review of medication and counseling by a nurse prior to discharge.[140] In the fourth study, although usual care included the pharmacist evaluating prescribed medications and clinical outcomes, they did not provide any form of counseling or advice to the patient.[142]

Outcome and Timing

None of the four studies reviewed here reported on the initiation of therapy. All studies examined and reported adherence-related outcomes.[139-142] Medication adherence was measured in different ways. One study used nonself-reported methods,[139] while three studies used self-report.[140-142] In the study that used nonself reported methods, medication adherence outcomes were obtained using pharmacy refill data.[139] In one study, exactly when outcomes were measured was unclear, although the references to "during the intervention year" indicated that various measurements were taken during the course of the intervention or immediately following it.[141] In another study, medication adherence outcomes focused on whether the patient took each medication as prescribed on the previous day.[140] In the other study, measurements were taken during the interventions, when pharmacists contacted the patients, but the exact timing was unclear.[139]

Setting

One study was set in nine pharmacies where pharmacists either called patients or faxed physicians.[139] Two studies were conducted within hospitals[140, 141] and one within community-based physician offices.[142] In one study, outcomes were measured at the completion of intervention (which was at the 12-month mark).[142]

Applicability

Limitations to applicability of interventions examined included studies where the level of involvement of pharmacists in the intervention arm was significantly greater than the currently accepted level of pharmacist involvement,[139] and where the intensity (duration and frequency of contact) of the multidisciplinary intervention may be high for routine or common use.[141]

Key Points

Overview

- Four studies provided mixed evidence on medication adherence, but no study suggested benefit from medication adherence interventions. The evidence suggests that pharmacist-led outreach, education, and problem-solving interventions have no benefit; we rated it as low strength of evidence. Due to lack of precision, we were unable to judge the true effect of case management and rated the evidence as insufficient.
- Because no study demonstrated improvement in medication adherence, we did not evaluate other outcomes.

Pharmacist-led Outreach, Education, and Problem-solving Interventions

- Medication adherence: the evidence, dominated by one study with a large sample size (more than 3,000 patients analyzed), suggests evidence of no benefit from pharmacist interventions directed at patients and providers on medication adherence (low strength of evidence). The same study, in a post hoc analysis indicated that the physician-directed intervention arm in the same study may be inferior to usual care in improving time to refill for medications.

Case Management Intervention

- Medication adherence: evidence was insufficient to grade.

Detailed Synthesis of Interventions for Unspecified or Multiple Chronic Conditions

Four studies, each dealing with populations with unspecified or multiple chronic conditions, met the inclusion criteria for our review.[139-142]

One study was directed at patients,[142] one at patients and providers,[139] and one at patients and systems.[140] One study, which used a multidisciplinary approach, was directed at systems-level change.[141]

No study found statistically significant differences in adherence between the intervention arm and the control arm (Table 73).[139-142] The pharmacists intervention suggested evidence of no benefit (Table 74).

Table 73. Unspecified or multiple chronic conditions: study characteristics

Author, Year N at Randomization	Population Setting	Intervention and Comparator
Nietert et al., 2009[139] N=3048	Patients who had a prescription written for diabetes mellitus, hypertension, hyperlipidemia, heart failure, depression, and/or psychoses; and who had at least two refills remaining for at least a 30-day supply Nine pharmacies within a medium-sized grocery store chain	G1: Phone Patient intervention—Grocery store pharmacists contacted overdue patients by telephone and reminded patients they were overdue, asked why patients were overdue, reminded them of the importance of taking their medication, and, when possible, helped patients find ways to overcome barriers to adherence in the future G2: Fax Physician intervention—Grocery store pharmacists faxed information to prescribing physicians about the study, written prompts to assist patients with adherence, and instructions to return patient disposition codes to store pharmacies via fax G3: Usual care involved filling prescriptions when requested by patients and arranging payment
Schnipper et al., 2006[140] N=178	Patients admitted on the general medicine service who were being discharged home and who could be contacted 30 days after discharge, spoke English; if cognitively impaired, they were included if they lived with someone who administered their meds regularly, could provide consent, and was willing to be the recipient of pharmacist interventions Hospital setting	G1: On the day of hospital discharge, a pharmacist reviewed each patient's discharge medication regimens with their pre-admission regimens and resolved discrepancies with a medical team; screened patient for previous drug-related problems (such as nonadherence), and reviewed the medication directions with the patient. During a follow-up phone call at 5 days postdischarge, pharmacist compared prescribed regimen with patient's self-reported medication list, screened for and resolved drug-related problems, and communicated results to patient's PCP G2: Routine review of medication orders by a ward-based pharmacist and medication counseling by a nurse at the time of discharge

Table 73. Unspecified or multiple chronic conditions: study characteristics (continued)

Author, Year N at Randomization	Population Setting	Intervention and Comparator
Sledge et al., 2006[141] N=96	Adults ≥18 years of age, with ≥2 medical or surgical hospital admissions during eligibility phase (12 months prior to patient selection efforts) Primary care center of an urban, academically affiliated hospital	G1: Comprehensive interdisciplinary medical and psychosocial assessment (2-3 hour visit, lifetime medical chart review, supplemental information from case manager, report to PCP), and ambulatory case management for 1 year in addition to usual care G2: Usual care directed by their PCP, including psychiatric consultation which was available on-site if requested by the PCP
Taylor et al., 2003[142] N=81	Adults ≥18 years of age who received care at the participating clinics and were identified as being at high risk for medication-related adverse events Community-based physician offices	G1: Patients in the intervention group received usual medical care, along with pharmacotherapeutic interventions by a pharmacist during regularly scheduled office visits. A patient typically met with a pharmacist for 20 minutes before seeing a physician. Interventions included clinical services and patient education but not dispensing. Pharmacists reviewed medical records and provided comprehensive individualized patient education that included a brief review of the disease, important lifestyle modifications, written materials, and basic drug information. Therapeutic recommendations were communicated to physicians through discussions or progress notes. In addition, the pharmacists monitored patients' responses to drugs and attempted to improve compliance by consolidating medication regimens, reducing dosage frequency, devising medication reminders, and teaching patients techniques for remembering. G2: Standard medical care without pharmaceutical care

Abbreviations: G, group; m, month; N, number; PCP, primary care physician.

Table 74. Multiple chronic conditions: medication adherence

Study N for Each Group N Analyzed	Adherence Measure Source/Method	Outcomes for Each Time Point
Nietert et al., 2009[139] N: 3048 G1: 1018 G2: 1016 G3: 1014	Time-to-refill (days) Pharmacy refill data/nonself-report	Unadjusted G1: Median (IQR), 108 (39 to 257) G2: Median (IQR), 116 (37 to 257) G3: Median (IQR), 106 (31 to 257) (257 represents a lower bound than 75th percentile because of amount of censoring present) 95% CI, NR p: NR Adjusted G1: HR 97.5% CI, 0.93 (0.82 to 1.06) G2: HR, 98.3% CI, 0.87 (0.76 to 1.00) G3: HR, 95% CI, 0.93 (0.83 to 1.05) 95% CI, NR p: NR

Table 74. Multiple chronic conditions: medication adherence (continued)

Study N for Each Group N Analyzed	Adherence Measure Source/Method	Outcomes for Each Time Point
G1: 1018 G2: 1016 G3: 1014	Filled prescription for any qualified medication in the same chronic disease classification as the index medication, within 30 days of index date	Unadjusted G1: N (%), 207 (20.3%) G2: N (%), 213 (21.0%) G3: N (%), 243 (24.0%) 95% CI, NR p: NR
	Pharmacy refill data/nonself-report	Adjusted G1: Hazard ratio (HR, 98.3% CI), 0.79 (0.61 to 1.03) G2: HR, 97.5% CI, 0.83 (0.65 to 1.06) G3: HR, 95.0% CI, 0.96 (0.77 to 1.20) 95% CI, NR p: NR
G1: 1018 G2: 1016 G3: 1014	Filled prescription for any qualified medication in the same chronic disease classification as the index medication, within 60 days of index date	Unadjusted G1: N (%), 348 (34.2%) G2: N (%), 342 (33.7%) G3: N (%), 373 (36.8%) 95% CI, NR p: NR
	Pharmacy refill data/nonself-report	Adjusted G1: Hazard ratio (HR, 97.5% CI), 0.86 (0.68 to 1.08) G2: HR, 98.3% CI, 0.83 (0.65 to 1.07) G3: HR, 95.0% CI, 1.03 (0.84 to 1.26) 95% CI, NR p: NR
G1: 1018 G2: 1016 G3: 1014	Filled prescription for any medication, within 30 days of index date Pharmacy refill data/nonself-report	Unadjusted G1: N (%), 460 (45.2%) G2: N (%), 484 (47.6%) G3: N (%), 490 (48.3%) 95% CI, NR p: NR
		Adjusted G1: Hazard ratio (HR, 98.3% CI), 0.86 (0.68 to 1.08) G2: HR, 95.0% CI, 0.99 (0.81 to 1.19) G3: HR, 97.5% CI, 0.87 (0.70 to 1.08) 95% CI, NR p: NR
Schnipper et al., 2006[140] G1: 92 G2: 84	Medication Adherence Score on previous day	G1: 88.9 (0.71 to 1.00) G2: 87.5 (0.73 to 1.00) 95% CI, NR p: 0.91
	Whether patient took each medication exactly as prescribed on previous day	(0 – 100; 100 represents complete adherence with all medications)
G1: 67 G2: 62	Number of patients nonadherent with at least one medication/Self-report	G1: 36 (54%) G2: 33 (53%) 95 % CI, NR p>0.99
	NR	
Sledge et al., 2006[141] G1:NR G2: NR	Medication Adherence Score Self-report	G1: NR G2: NR p: NR; nonsignificant

Table 74. Multiple chronic conditions: medication adherence (continued)

Study N for Each Group N Analyzed	Adherence Measure Source/Method	Outcomes for Each Time Point
Taylor et al., 2003 [142] Overall N: 69 G1: 33 G2: 36	Compliance Took ≥80% of all medications in past month/self-report	12 months: Mean (SD) compliant patients G1: 100 G2: 88.9 (6.3) 95% CI, NR p: 0.115

Abbreviations: CI, confidence interval; G, group; HR, hazard ratio; IQR, interquartile range; N, number, NR, not reported.

Table 75. Pharmacist-led outreach, education, and problem-solving interventions for unspecified or multiple chronic conditions: strength of evidence

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Pharmacist-based intervention (Phone-patient or based on Fax physician) vs. usual care	3; 3224+NR N in one study	Persistence of prescription refills (number of days from recommended refill date)	RCT Medium	Unknown	Indirect	Imprecise	No significant difference in time to refill across arms. Low SOE of no benefit
	0	Mortality	NA	NA	NA	NA	Insufficient
	0	Biomarkers	NA	NA	NA	NA	Insufficient
	0	Morbidity	NA	NA	NA	NA	Insufficient
	0	Patient satisfaction	NA	NA	NA	NA	Insufficient
	0	Quality of life	NA	NA	NA	NA	Insufficient
	0	Health care utilization	NA	NA	NA	NA	Insufficient
	0	Quality of care	NA	NA	NA	NA	Insufficient

Abbreviations: N: number; NA, not applicable; NR: not reported; RCT, randomized controlled trial; SOE, strength of evidence.

Key Question 2. Summary of Policy-Level Interventions: Medication Adherence and Other Outcomes

This key question evaluates the effect of policy interventions on medication adherence. We first present a description of the included studies, followed by key points for the body of evidence. We do not present a detailed overall synthesis; instead, we present results by clinical condition, for diabetes, cardiovascular disease, and reactive airway disease. For each section, we briefly recap the description of included studies, then present key points and provide a detailed synthesis of included studies. Table 76 presents study characteristics. Table 77 through Table 82 present results and strength of evidence for diabetes, cardiovascular disease, and reactive airway disease. All disease-specific tables follow the detailed synthesis of results for that condition.

Description of Included Studies

Overview

Three studies evaluated the effects of policy interventions on medication adherence.[146-148] All three studies were prospective cohort studies with a medium risk of bias.

Population, Intervention, and Comparator

Two of these studies examined the effect of reduced medication copays. One study evaluated the effects of reduced copays for medications in five classes (i.e., angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers, beta-blockers, diabetes medications, 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors, and inhaled corticosteroids) for employees and the covered dependents of a large company that used a specific disease management program.[146] This study compared the outcomes from the policy change with outcomes for employees and covered dependents of another large employer that used the same disease management program but kept medication copays stable during the study. This study was limited to adults ages 18 to 64. The other study examined the effects of reduced copays for statins and clopidogrel for beneficiaries of Pitney Bowes, a large company located in New Jersey.[147] This study compared outcomes from the policy change with outcomes for beneficiaries of Horizon Blue Cross Blue Shield of New Jersey, which uses the same pharmacy benefit manager as Pitney Bowes but maintained stable medication copays during the study. Although this study did not impose age restrictions, the mean age ranged from 53.8 to 67.5 across groups.

Another study examined the impact of Medicare Part D on medication adherence among adults ages 65 or older with hyperlipidemia, hypertension, and/or diabetes.[148] The study restricted participants to those who were continuously enrolled in a large Pennsylvania insurer's Medicare Advantage products between 2003 and 2007.[148] The study had three groups that varied in their level of coverage for prescription medications before the introduction of Medicare Part D; the prior coverage ranged from no coverage to a $350 quarterly cap on costs that were covered by the insurance provider. Thus, individuals in these three groups experienced an improvement in coverage when Medicare Part D was introduced. The study also had a comparison group of individuals with retiree health insurance that almost always provided more generous coverage for prescription medications than offered by Medicare Part D plans. Thus, individuals in the comparison group did not experience improved prescription drug coverage following implementation of Medicare Part D.

Table 76. Policy interventions: study characteristics

Author, Year N at Baseline	Population; Setting	Intervention and Comparator
Chernew et al., 2008[146] N=NR	Adults, ages 18-64; Employee health plan	G1: Employer-based health insurance plan implemented policy to reduce copayments for five chronic medication classes as part of a disease management program. Copays for generics were reduced to zero, copays for brand-name medications were reduced by half of previous value. G2: No reduction in copays
Choudhry et al., 2010[147] N=52,631	Patients with prescription claims for a statin or clopidogrel; pharmacy benefits management organization	G1: Elimination of copayments for statins for company employees and beneficiaries with diabetes or vascular disease (Pitney Bowes) G2: Lowered copayments for all employees and beneficiaries prescribed clopidogrel (Pitney Bowes) G3: No change in copayments, statin users (BCBS of NJ) G4: No change in copay, clopidogrel users (BCBS of NJ)
Zhang et al., 2010[148] N=9185	Older adults enrolled in Medicare Part D Advantage products; Medicare enrollees	G1: No drug coverage prior to Medicare Part D G2: Some drug coverage prior to Medicare Part D with a $150 quarterly cap on plan payment G3: Some drug coverage prior to Medicare Part D with a $350 quarterly cap on plan payment G4: Comparison group, covered by retiree health benefits had no deductible, paid copayments of $10–$20 per monthly prescription. No change in benefits during study

Abbreviations: BCBS, Blue Cross/Blue Shield; G, group; N, number; NJ, New Jersey; NR, not reported.

Outcome and Timing

In two studies, the investigators tracked medication adherence for 1 year before and 1 year after the change in copay using the medication possession ratio (MPR).[146, 147] The other study tracked the MPR for 4 years, 2 years before and 2 years after the introduction of Medicare Part D.[148]

Applicability

We rated all three studies as broadly applicable to intervention and outcomes and two of the studies[146, 147] as broadly applicable to the remaining criteria considered (i.e., population, comparator). We rated the remaining study as potentially less applicable to population and comparator because the study was limited to individuals who were continuously enrolled in a Medicare Advantage plan from 2004 through 2007.[148] In 2004, only 13 percent of Medicare beneficiaries were enrolled in such plans.[149]

Key Points

- All three studies found statistically significant between-group differences in adherence to most of the medications investigated following intervention implementation.
- In two studies,[146, 147] medication adherence decreased over time in both intervention and comparisons groups. Thus, the between-group differences observed were caused by a difference in the extent to which adherence declined.
- Among individuals with no previous prescription drug coverage, implementation of Medicare Part D was associated with a large improvement in medication adherence.
- Among individuals with previous prescription drug coverage, the effects observed following implementation of Medicare Part D were similar to those observed in the studies examining the effects of medication copay reductions.
- Among patients with cardiovascular disease or diabetes, results from three observational studies with consistent results suggest that policy interventions can have beneficial effects on medication adherence (moderate strength of evidence).
- Among patients with respiratory conditions, evidence is insufficient to assess the effect of policy interventions on medication adherence.
- None of the studies examined the effect of the interventions on more distal outcomes (e.g., morbidity, mortality, health service utilization).

Interventions for Diabetes

Description of Included Studies

Two studies evaluated the effects of policy interventions on adherence to medications used to treat diabetes (Table 76). One study examined the effect of reduced medication copays.[146] The other study examined the impact of Medicare Part D on medication adherence among adults ages 65 or older.[148]

Key Points

- Both studies found statistically significant differences in medication adherence between the intervention and comparison groups following intervention implementation.
- In the study that examined reduced medication copays, medication adherence decreased over time in both intervention and comparisons groups. However, adherence decreased less among individuals in the reduced-copay group than among individuals in the comparison group.
- Implementation of Medicare Part D had the greatest impact among individuals who had no previous prescription drug coverage.
- We found moderate strength of evidence for benefits to medication adherence based on two observational studies with consistent results.
- Neither study examined the effect of the interventions on more distal outcomes (e.g., morbidity, mortality, health service utilization).

Detailed Synthesis

One study examined the effects of reduced medication copays on medication adherence using pharmacy claims data to calculate the MPR.[146] Although this study found a between-group difference of 4.02 MPR percentage points (Table 77), favoring the reduced copay group, medication adherence decreased over time in both groups. More specifically, among individuals in the reduced copay group, medication adherence decreased from approximately 67 percent at baseline to approximately 60 percent at final followup; whereas, among individuals in the comparison group, medication adherence decreased from approximately 79 percent at baseline to approximately 68 percent at final followup. Thus, the between-group difference observed was due to the slower rate of decline in MPR in the intervention group relative to the comparison group. Moreover, the comparison group had a higher mean MPR at the end of followup than the intervention group. Therefore, we cannot draw firm conclusions from this study (Table 78).

The study that examined the impact of Medicare Part D on adherence to diabetes medications reported consistent improvements in medication adherence following the implementation of Medicare Part D, particularly among people who had not previously had any type of prescription drug coverage.[148] More specifically, MPR increased 17.9 more points among individuals who did not have any prescription drug coverage before Medicare Part D than among individuals in the comparison group (Table 77). Among patients who had had some coverage for prescription medications before Medicare Part D, the study estimated differences in MPR scores of about 4 points. This dose-response relationship (i.e., adherence increased most among individuals with the greatest improvement in benefits) supports the conclusion that improved prescription drug coverage has a beneficial effect on medication adherence (Table 78).

Table 77. Policy interventions for diabetes: medication adherence

Study N for Each Group	Adherence Measure Source/Method	Outcomes
Chernew et al., 2008[146] 2004 (pre) G1: range 919–1,245 G2: range 3,596–4,185 2005 (post) G1: range 1,056–1,306 G2: range 3,535–4,072	Medication possession ratio/ Prescription claims data	Difference in % of days covered (MPR points) Diabetes drugs: 4.02, p<0.001
Zhang et al, 2010[148] Diabetes G1: 247 G2: 304 G3: 2,214 G4: 1,253	Medication possession ratio/Prescription claims data	Change in % of days covered (MPR points): Estimate (95% CI) Diabetes G1: 17.9 (13.7 to 22.1) G2: 4.5 (1.0 to 7.9) G3: 3.6 (1.8 to 5.3) G4: 0 (Ref)
Diabetes G1: 247 G2: 304 G3: 2,214 G4: 1,253	Medication possession ratio ≥ 0.80/Prescription claims data	Adjusted odds ratio (95% CI) Diabetes G1: 2.36 (1.81 to 3.08) G2: 1.17 (0.9 to 1.51) G3: 1.21 (1.06 to 1.39) G4: 1.00 (Ref)
Diabetes G1: 247 G2: 304 G3: 2,214 G4: 1,253	Treatment intensity/Prescription claims data	Change in average number of pills for condition taken per day: Effect (95% CI) Diabetes G1: 0.184 (0.1 to 0.27) G2: 0.095 (0.03 to 0.16) G3: 0.02 (-0.01 to 0.05) G4: 0 (Ref)

Abbreviations: CI, confidence interval; G, group; MPR, medication possession ratio; N, number.

Table 78. Policy interventions for diabetes: strength of evidence

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Confounding	Magnitude of Effect/Strength of Evidence
Improved prescription drug coverage vs. Unchanged prescription drug coverage	2; ~13,000 (~13,000)	Medication adherence	Medium	Consistent	Direct	Precise	Present	Gaining coverage for diabetes medications 17.9 MPR points Reduced copay or improvement of previous coverage About 4 MPR points/ Moderate

Abbreviations: MPR, Medication possession ratio

Interventions for Cardiovascular Disease

Description of Included Studies

All three policy-level studies evaluated the effects of policy interventions on adherence to medications used to treat cardiovascular diseases (Table 79).

Key Points

- All three studies found statistically significant differences in medication adherence between the intervention and comparison groups following intervention implementation.
- In two studies, medication adherence decreased over time in both intervention and comparisons groups. Thus, the between-group differences observed were caused by a difference in the extent to which adherence declined.
- We found moderate strength of evidence for benefits to medication adherence based on three observational studies with consistent results.
- None of the studies examined the effect of the interventions on more distal outcomes (e.g., morbidity, mortality, health service utilization).

Detailed Synthesis

Three studies examined the effect of policy interventions on adherence to medications used to treat cardiovascular diseases (Table 79). Two of these studies examined the effects of reduced medication copays.[146, 147] Their methods were similar—using pharmacy claims data to calculate either the MPR or proportion of days covered (PDC); both measures reflect the days of medication supply obtained during a specified period of time divided by the number of days in the period. Both studies performed analyses using MPR or PDC as a continuous measure and found between-group differences, favoring the intervention group, that ranged from 2.59 to 4.2 percentage points. Nonetheless, medication adherence decreased over time in both studies in both the intervention and comparison groups. For example, one study reported MPR scores for statins and clopidrogel ranging across study groups from about 80 to 87 percent at baseline and from about 63 percent to 67 percent at followup.[147] The other study did not report specific MPR scores at followup.[146] Choudhry et al. also dichotomized PDC at (1) below 0.8 or (2) at or above 0.8.[147] In these analyses, individuals in the intervention group had 17.0 percent to 19.9 percent greater odds of high adherence relative to individuals in the comparison group immediately following the copay reduction. Thereafter, the magnitude of the between-group difference remained stable over time.

Despite these positive findings, both studies used observational research designs and had comparison groups that differed on numerous characteristics from the intervention group. In addition, one study lacked sufficient detail to permit us to evaluate fully the analytic methods used.[146] Finally, in one study, medication copays increased for clopidogrel in the comparison group.[147] Therefore, we cannot determine whether the effects observed could be attributed to the decrease in copay in the intervention group, the increase in copay in the comparison group, or a combination of the two changes. These factors weaken the evidence that decreasing medication copays has a beneficial effect on medication adherence (Table 80).

The final study examined the impact of Medicare Part D on medication adherence (Table 79).[148] In contrast to the findings from the two studies already discussed, this study found consistent improvements in medication adherence following intervention implementation,

particularly among people who had not previously had any type of prescription drug coverage. For example, in analyses focusing on medications used to treat hyperlipidemia, MPR increased 13.4 more points among individuals who did not have prescription drug coverage before Medicare Part D than among individuals in the comparison group. The study found a similar difference among patients with hypertension. However, among patients with some coverage for prescription medications, the study estimated differences in MPR scores ranging from 2.5 to 7.3. This dose-response relationship (i.e., adherence increased most among individuals with the greatest improvement in benefits) supports the conclusion that improved prescription drug coverage has a beneficial effect on medication adherence (Table 80).

Table 79. Policy interventions for cardiovascular disease: medication adherence

Study N for Each Group	Adherence Measure Source/Method	Outcomes
Chernew et al., 2008[146]	Medication possession ratio/ Prescription claims data	Difference in % of days covered (MPR points) ACE inhibitors/ARBs: 2.59, p<0.001 Beta-blockers: 3.02, p<0.001 Statins: 3.39, p<0.001
Choudhry et al., 2010[147] G1: 2,051 G2: 779 G3: 38,174 G4: 11,627	Proportion of days covered (PDC)/ Prescription claims data	Statin users G1: Immediate 3.1% higher PDC relative to G3 following copay reduction, with no subsequent change in slope over 12 months of followup; 95% CI, NR; p: <0.05 Clopidogrel users G2: Immediate 4.2% higher PDC relative to G4 following copay reduction, with no subsequent change in slope over 12 months of followup; 95% CI, NR; p: <0.05
G1: 2,051 G2: 779 G3: 38,174 G4: 11,627	Odds of PDC ≥ .80/ Prescription claims data	Statin users G1: Immediate 17.0% change in odds of adherence relative to G3 following copay reduction, with no subsequent change in slope over 12 months of followup; 95% CI, NR; p: <0.05 Clopidogrel users G2: Immediate 19.9% change in odds of adherence relative to G4, with no subsequent change in slope over 12 months of followup; 95% CI, NR; p:<0.05
Zhang et al., 2010[148] Hyperlipidemia G1: 418; G2: 647 G3: 5,093; G4: 3027	Medication possession ratio /Prescription claims data	Change in % of days covered (MPR points): Estimate (95% CI) Hyperlipidemia G1: 13.4 (10.1 to 16.8) G2: 7.3 (4.8 to 9.8) G3: 4.4 (3.3 to 5.6) G4: 0 (Ref)
Hypertension: G1: 980; G2: 1234 G3: 8,380; G4: 4141	Medication possession ratio /Prescription claims data	Hypertension G1: 13.5 (11.5 to 15.5) G2: 2.6 (1.2 to 4.1) G3: 2.5 (1.7 to 3.2) G4: 0 (Ref)

Table 79. Policy interventions for cardiovascular disease: medication adherence (continued)

Study N for Each Group	Adherence Measure Source/Method	Outcomes
Hyperlipidemia G1: 418; G2: 647 G3: 5,093; G4: 3027	Medication possession ratio ≥ 0.80/Prescription claims data	Adjusted odds ratio (95% CI) Hyperlipidemia G1: 1.67 (1.35 to 2.07) G2: 1.22 (1.04 to 1.43) G3: 1.14 (1.06 to 1.24) G4: 1.00 (Ref)
Hypertension: G1: 980; G2: 1234 G3: 8,380; G4: 4141	Medication possession ratio ≥ 0.80/Prescription claims data	Hypertension G1: 2.09 (1.82 to 2.40) G2: 1.13 (0.99 to 1.29) G3: 1.14 (1.05 to 1.23) G4: 1.00 (Ref)
Hypertension: G1: 980; G2: 1,234 G3: 8,380; G4: 4,141	Treatment intensity/Prescription claims data	Change in average number of pills for condition taken per day: Effect (95% CI) Hypertension G1: 0.221 (0.16 to 0.28) G2: 0.054 (0.02 to 0.09) G3: 0.028 (0.01 to 0.05) G4: 0 (Ref)

Abbreviations: ACE Inhibitors, Angiotensin-converting enzyme inhibitors; CI, Confidence interval; G, group; MPR, Medication possession ratio; N, number; NR, Not reported.

Table 80. Policy interventions for cardiovascular disease: strength of evidence

Intervention	Number of Studies; Subjects (Analyzed)*	Outcome	Risk of Bias	Consistency	Directness	Precision	Confounding	Magnitude of Effect/ Strength of Evidence
Improved prescription drug coverage vs. Unchanged prescription drug coverage	3; Over 61,000 (Over 61,000)	Medication Adherence	Medium	Consistent	Direct	Precise	Present	Magnitude of effect varies depending on the degree to which coverage is improved/ Moderate

Interventions for Reactive Airway Diseases: Medication Adherence and Other Outcomes

Description of Included Studies

One study examined the effect of reduced medication copays on adherence to inhaled corticosteroids (Table 81).[146]

Key Points

- The intervention had no effect on adherence to inhaled corticosteroids.
- Evidence is insufficient to draw a conclusion regarding the effect of reduced copays on adherence to medications used to treat respiratory conditions.

Detailed Synthesis

The study provided very little information about the characteristics of members in the two health plans compared. Therefore, we are unable to determine the extent to which unmeasured confounders may have affected study findings. Although the article stated that the MPR for inhaled corticosteroids was 31.56 at baseline, it did not provide this information by study group. In addition, the study did not report the number of study participants using inhaled corticosteroids (Table 81). Therefore, we cannot determine whether lack of power may have contributed to the null findings reported (Table 82).

Table 81. Policy interventions for reactive airway diseases: medication adherence

Study N for Each Group	Adherence Measure Source/Method	Outcomes
Chernew et al., 2008[146] N: NR	MPR/Prescription claims data	Change in % of days covered (Possible range 0 to 100%) Inhaled corticosteroids: 1.86, p<0.134

Abbreviations: MPR, Medication Possession Ratio; N, number; NR, not reported.

Table 82. Policy interventions for reactive airway diseases: strength of evidence

Intervention	Number of Studies; Subjects (Analyzed)*	Outcome	Risk of Bias	Consistency	Directness	Precision	Confounding	Strength of Evidence
Reduced medication copay vs. Unchanged medication copay	1; NR (NR)	Medication Adherence	High	Unknown	Direct	Unknown	Present	Insufficient

Abbreviations: NR, not reported.

Key Question 3. Intervention Characteristics and Outcomes For Direct Comparisons of Intervention Characteristics

Key Question (KQ) 3a, which addresses intervention characteristics as noted earlier, includes all studies relevant for KQ 1 and KQ 2. These studies are described in detail in earlier sections of the report. We present our results for intervention characteristics first for all included studies for this report, followed by results for the small subset of studies that directly compared intervention elements (KQ 3b).

Key Question 3a. Intervention Characteristics

Description of Included Studies

Earlier sections of the report provide a detailed description of all 57 studies (63 articles) included in KQ 1 and KQ 2. We present key points below, followed by a detailed synthesis for KQ 3.

Key Points

- The studies of adherence interventions that we included varied by six key characteristics: (1) intervention target; (2) intervention agent; (3) intervention mode; (4) intensity (total time and frequency); (5) duration of intervention delivery; and (6) intervention components.
- We included studies that did not use consistent language or taxonomy to describe the interventions that they were testing.
- About half of the adherence interventions were delivered by a pharmacist, physician, or nurse.
- About half of the adherence interventions involved face-to-face contact.
- The majority of interventions incorporated more than one component.
  Nurses, multidisciplinary teams (often including nurses), automated systems, and other nonphysician/nonpharmacist health professionals tended to combine delivery of knowledge-based components with components that also raised clients' self-awareness more than did physician or pharmacist-delivered interventions.

Detailed Synthesis of Intervention Characteristics

Overview of Characterization of Interventions

Below we have characterized the interventions tested in the studies reviewed based on several features to answer the question, "How do medication-adherence intervention characteristics vary?" Based on a review of 57 studies that tested interventions to improve medication adherence, we identified six key characteristics by which interventions typically varied: (1) intervention target; (2) agent delivering the intervention; (3) mode of delivery; (4) intensity of the intervention; (5) duration of the intervention; and (6) intervention components. Below we define each characteristic and describe the interventions identified in the literature based on these characteristics. In Figure 3, we depict the distribution of intervention characteristics in relation to each other, including intervention target, agent, and mode of delivery. We then describe the components of the interventions based on a taxonomy developed by deBruin and colleagues.[70]

Intervention Target

Intervention target refers to the person, people, health system, or policy to which intervention activities are directed. Although the ultimate goal of adherence interventions is to improve patient behavior (i.e., taking medications), the interventions may do this by directly targeting providers, patients, health systems, health policies, or some combination of these four. In the 57 studies we reviewed, we identified seven individual or combinations of intervention targets to which at least one intervention was directed. These were (in order of frequency): (1) patients only (39 percent of interventions); (2) combination of patients, providers, and systems (25 percent); (3) combination of patients and systems (21 percent); (4) combination of patients and providers (7 percent); (5) providers only (1.7 percent); (6) systems only (1.7 percent); and (7) health policy changes (5 percent). In sum, over one third of medication adherence interventions tested in trials targeted only patient factors and hence not the full spectrum of many factors that are known to interfere with adherence, which also includes provider, system and policy level barriers.

Intervention Agent

Intervention agent refers to the person, people, or technology used to deliver the intervention. Like intervention targets, the agents that delivered the interventions varied widely and did not appear to be highly correlated with the type of target to which the intervention was directed. In total, of the 57 interventions reviewed (in order of frequency), 12 (21 percent) were delivered by pharmacists, 9 (16 percent) were delivered by nurses, 7 (11 percent) were delivered by physicians (including one physician administrator), 6 (11 percent) by an automated system, 5 (9 percent) by a multidisciplinary team, 2 (3.5 percent) by care managers, 1 (1.7 percent) by a medical assistant, and 1 (1.7 percent) by a health coach. Other agents included a health educator, a psychologist, a counselor, research staff members, and some audio-video materials. For 7 interventions (11 percent), including the 3 directed at policy changes, a specific agent of delivery was not applicable or identifiable.

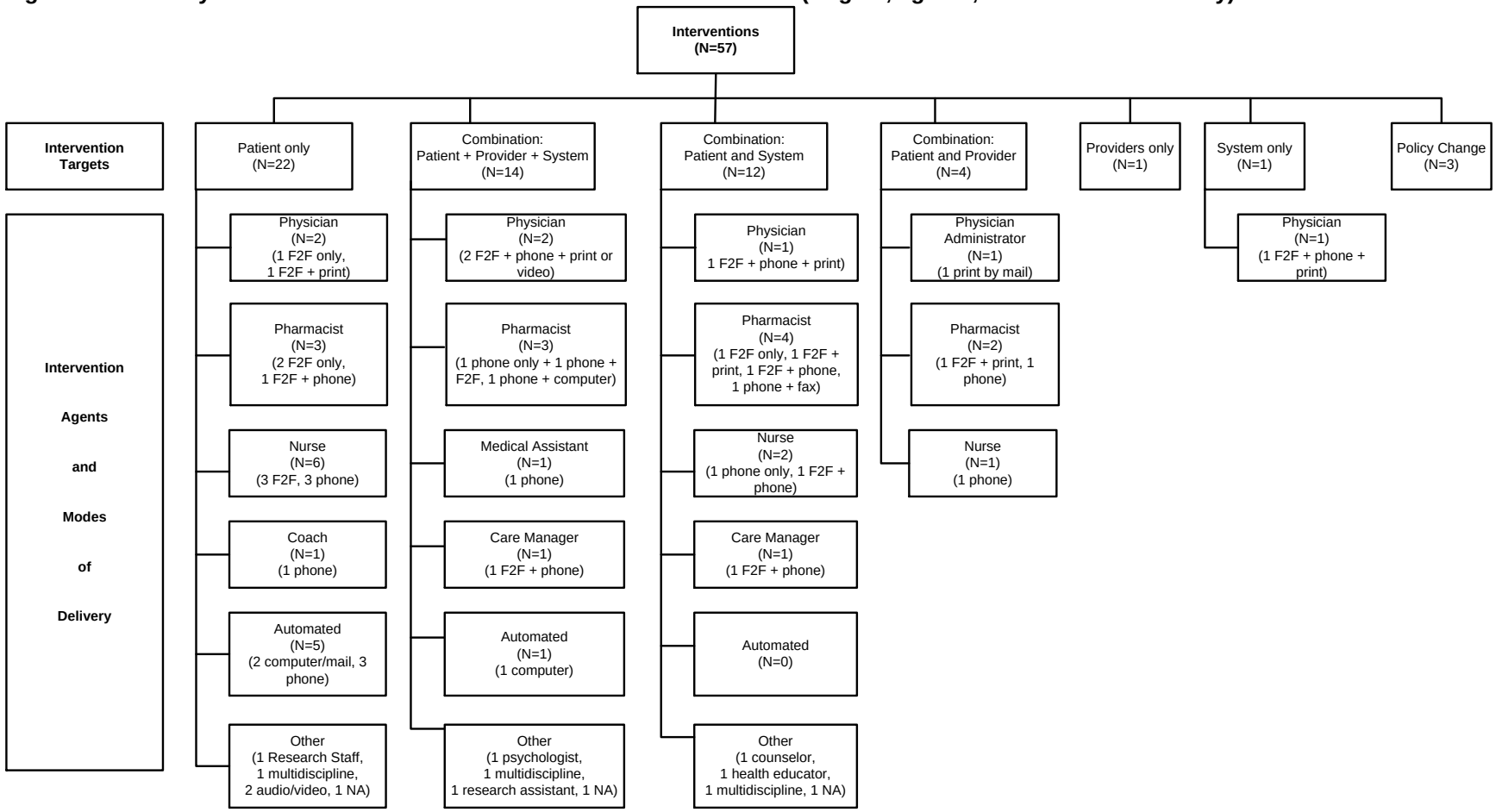
Interventions that targeted "patients only" tended to use automated (23 percent) and nurse (27 percent) agents more than did interventions that targeted combinations of factors. In contrast, few interventions with a combination of targets used automated systems (4 percent) or nurses (8 percent) as agents. Moreover, physicians or pharmacists delivered interventions that targeted "patients only" (23 percent) less often than the interventions that targeted combinations of factors (38 percent). Despite these few specific observations, both targets and agents of delivery were varied overall.

Mode of Delivery

Mode of delivery refers to the manner by which the agent delivers the intervention, such as face-to-face, over the phone, using print materials, by computer, on a DVD, video, or CD/audio or a combination of these modes. Of the 57 interventions, 24 (52 percent) of the interventions involved only 1 delivery mode and 21 (37 percent) utilized 2. Five (9 percent) used 3 delivery modes and four (7 percent) used 4 modes to deliver the intervention.

Twenty-eight of the interventions (49 percent) involved at least some face-to-face contact although, of these 28, 20 (71 percent) combined face-to-face with additional modes of delivery, such as phone contact, print materials, computer, video, or other materials. Similarly, 30 interventions (53 percent) delivered at least some of the intervention by phone; however, only 13 (43 percent) of these involved "phone-only" delivery modes. Eighteen or about one third (32 percent) of the interventions used print material, although only 5 (28 percent) of these 18 utilized print materials alone, all of which were mailed to their targets. Six of the 57 interventions (11 percent) were at least partially delivered by computer, with only 2 being entirely computer delivered. Seven interventions (12 percent) involved audio or video/DVDs with only 2 (3.5 percent) delivered solely by audio or video/DVD. One intervention (1.7 percent) used a medication dosing aid device to deliver part of the intervention. , Another intervention which simply involved a novel blister packaging mechanism did not have clear agent or mode of delivery.

Figure 3. Summary of medication adherence intervention characteristics (targets, agents, and modes of delivery)



Abbreviation: F2F, face-to-face; assist, assistant

Intensity of the Intervention

The intensity of an intervention refers to the frequency and total amount of time an intervention takes. It is determined by summing the duration of each individual session for the total number of sessions. Hence, as shown in Table 83, the interventions' intensities can vary in: (1) the total number of contacts; (2) the frequency with which contacts were delivered; (3) the total number of minutes of contact time; and (4) the duration of calendar time over which the intervention was delivered.

Number and Frequency of Contacts

As seen in Table 83, in 4 studies, the intervention did not involve specific contact points (such as with a systems or policy change) and in 4 other studies, information about the number of contacts was not specified. Among those that provided such information, the number of contacts ranged from 1 to 30. As might be expected, interventions with higher numbers of contacts often were solely or at least partially delivered by phone. Many face-to-face interventions, however, included as many as 5 to 6 contacts. Interventions that involved more than one contact varied not only by number of contacts but also by the frequency of delivery. Frequencies ranged from as often as daily to as infrequently as every 3 months, although most were delivered weekly to monthly.

Total Amount of Contact Time

Twenty-nine studies (51 percent) did not specify the total dose intensity of the interventions; another 6 (11 percent) gave only the minimum amount of the intervention (e.g., 120+ minutes, at least 2.5 hours, etc.) or specified only the amount per contact but did not give the number of contacts (Table 83). Among the studies that provided this information, the amount of time varied widely among interventions, ranging from 6 minutes to 12 hours. Of those 26 that provided information regarding at least the minimum amount of total contact time, 15 (58 percent) were less than 120 minutes in total time; 6 (23 percent) were more than 180 minutes in total time.

While only a limited number of conclusions can be drawn due to the large number of studies not reporting total contact time, the overall duration of the program does not appear to be strongly associated with the total intensity of time. For example, in comparing three asthma studies, one study lasting 10 weeks had a total intensity of only 15 minutes while another lasting 7 weeks had a total intensity of 150 minutes, and yet a third lasting 9 months had a just slightly greater intensity at 210 minutes.

Intervention Duration

As with frequency, reporting of calendar time was not relevant for the interventions that were delivered during a single contact episode. Several others did not specify the duration of the program in calendar time. Of the 37 interventions (65 percent) that did, the duration ranged widely from 4 weeks to 2 years, with 6 months' duration as the mode: 10 (27 percent) of the 37 studies lasted 6 months. Another 7 (19 percent) of programs with known duration lasted 12 months, 5 (about 14 percent) lasted 3 months, and only 2 (5 percent) lasted 2 years. Duration of the remaining 13 interventions (35 percent) fell between 4 weeks and 12 months. In general, asthma and congestive heart failure medication adherence interventions appeared to be of slightly shorter duration compared with those for diabetes, depression, hypertension, and hypercholesterolemia.

Table 83. Delivery mode, number of contacts, frequency, total time, and calendar duration of interventions reviewed by chronic medical condition

Citation	Condition	Mode	N	Frequency	Total minutes	Duration
Janson et al., 2003[118]	Asthma	F2F	5	NS	150 minutes	7 weeks
Berg et al., 1997[119]	Asthma	F2F	6	NS	720 minutes	7 weeks
Janson et al., 2009[116]	Asthma	F2F	5	q 2-4 weeks	150 minutes	14 weeks
Wilson et al., 2010[122]	Asthma	F2F, phone	5	NS	210 minutes	9 months
Weinberger et al., 2002[120]	Asthma	F2F, print	.> 1 NS	q month	NS	NS
Weinberger et al., 2002[120]	Asthma	F2F, print	> 1 NS	q month	NS	NS
Bender et al., 2010[115]	Asthma	Phone	2-3	NS	~10-15 minutes	10 weeks
Bender et al., 2010[115]	Asthma	Phone	2-3	NS	~10-15 minutes	10 weeks
Schaffer & Tian, 2004[117]	Asthma	Audio or book	1	NA	30-60 minutes	NS
Williams et al., 2010[121]	Asthma	Computer	> 1 NS	q 2 weeks	NS	NS
Murray et al., 2007[111]	Congestive heart failure	F2F, print	NS	NS	NS	9 months
Rich et al., 1996[112]	Congestive heart failure	F2F, print	NS	NS	NS	NS
Fulmer et al., 1999[110]	Congestive heart failure	Phone, videophone	30	q day	~120 minutes	6 weeks
Ross et al., 2004[113]	Congestive heart failure	Computer	NS	NS	NS	12 months
Bogner & de Vries, 2010[84]	Depression, Diabetes	F2F, phone	5	NS	120 minutes	4 weeks
Bogner & de Vries, 2008[97]	Depression	F2F, phone	5	NS	120 minutes	4 weeks
Katon et al., 2001[125] Ludman et al., 2003[126] Von Korff et al., 2003[127]	Depression	F2F, phone, print, DVD	9	NS	150+ minutes	12 months
Katon et al., 1999[132] Katon et al., 2002[131]	Depression	F2F, phone, print, DVD	2+	NS	75 minutes	NS
Katon et al., 1996[130]	Depression	F2F, phone, print, videos	8	q 2-12 weeks	360+ minutes	24 weeks
Katon et al., 1995[129]	Depression	F2F,print, video	4	q 8-10 days	105 minutes	6 weeks
Simon et al., 2006[124]	Depression	Phone	3	q 1-2 month	60 minutes	3 months
Capoccia et al., 2004[128]	Depression	Phone	18	q 1-2 week	270 minutes	12 months
Pyne et al., 2011[133]	Depression	Phone [for Pat] EMR [for Prov]	> 1 NS	q 2-4 weeks	NS	NS
Rickles et al., 2005[123]	Depression	Phone	3	NS	45 minutes	3 months
Hoffman et al., 2003[134]	Depression	Print, mail	6	q month	NS	6 month
Weymiller et al., 2007[86] Jones et al., 2009[87]	Diabetes	F2F	1	NA	NS	NA
Pearce et al., 2008[90]	Diabetes	F2F	1	NA	30 minutes	NA

Table 83. Delivery mode, number of contacts, frequency, total time, and calendar duration of interventions reviewed by chronic medical condition (continued)

Citation	Condition	Mode	N	Frequency	Total minutes	Duration
Lin et al., 2006[83]	Diabetes	F2F, phone	16	NS	240+minutes	12 months
Mann et al., 2010[88] Choice	Diabetes	F2F, print	1	NA	6 minutes	NA
Mann et al., 2010[88] Choice	Diabetes	F2F, print	1	NA	6 minutes	NA
Grant et al., 2003[85]	Diabetes	Phone, computer	6	Q 2 weeks	111 minutes	3 months
Okeke et al., 2009[135]	Glaucoma	F2F, phone, video, dosing aid device	10	NS	NS	3 months
Schectman et al., 1994[92]	Hypercholesterolemia	Phone	5	NS	NS	28 days
Stacy et al., 2009[93]	Hypercholesterolemia	Phone, mail, print	3	NS	NS	6 months
Guthrie, 2001[91]	Hypercholesterolemia	Phone, mail	5	Per schedule	NS	6 months
Johnson et al., 2006[94]	Hypercholesterolemia	Computer; mail	3	NS	NS	6 months
Hunt et al., 2008[104]	Hypertension	F2F	1-4	NS	NS	NS
Lee et al., 2006[74]	Hypertension, Hyperlipidemia	F2F	7	q 2 months	240 minutes	12 months
Vivian, 2002[107]	Hypertension	F2F	6	NS	NS	6 months
Carter et al., 2009[103]	Hypertension	F2F, phone	1.6	q 3 month	NS	6 months
Solomon et al., 1998[105] Gourley et al., 1998[106]	Hypertension, COPD	F2F, phone	5	NS	NS	6 months
Rudd et al., 2004[102]	Hypertension	Phone	5	Per schedule	NS	4 months
Bosworth et al., 2008[98] Bosworth et al., 2007[99]	Hypertension	Phone	12	Q 2 month	NS	24 months
Bosworth et al., 2005[100]	Hypertension	Phone	12	Q 2 month	NS	24 months
Friedman et al., 1996[101]	Hypertension	Phone	24	Weekly	96 minutes	6 months
Johnson et al., 2006[108]	Hypertension	Computer; mail	3	q 3 months	NA	6 months
Schneider et al., 2008[109]	Hypertension	Packaging	NA	NA	NA	NA
Rudd et al., 2009[137]	Inflammatory arthritis	F2F, phone, print	2	q month	40 minutes	NS
Powell et al., 1995[95]	Multiple chronic conditions	Mail	1	NA	30 minute	NA
Zhang et al., 2010[148]	Multiple chronic conditions	NA	NA	NA	NA	NA
Chernew et al., 2008[146]	Multiple chronic conditions	NA	NA	NA	NA	NA
Nietert et al., 2009[139]	Multiple chronic conditions	Telephone, fax	NS	NS	NS	NS

Table 83. Delivery mode, number of contacts, frequency, total time, and calendar duration of interventions reviewed by chronic medical condition (continued)

Citation	Condition	Mode	N	Frequency	Total minutes	Duration
Choudhry et al., 2010[147]	Multiple conditions	NA	NA	NS	NA	NA
Berger et al., 2005[136]	Multiple sclerosis	Phone	6-12	q 2-4 weeks	NS	3 months
Waalen et al., 2009[138]	Osteoporosis	F2F, phones, print	varied	q month	5-minute/call	NS
Taylor et al., 2003[142]	Other	F2F, print	>1 NS	NS	20-minute/visit	12 months
Sledge et al., 2006[141]	Other	F2F, phone, print	> 13	Monthly phone	180+ minutes	1 year
Schnipper et al., 2006[140]	Other	F2F, phone	2	NS	NS	NS

Abbreviations: COPD, chronic obstruction pulmonary disease; DVD, optical disc storage media format; EMR, electronic medical record; F2F, face-to-face; N, number; NA, not applicable; NS, not specified; Q/q, every.

Taxonomy of Adherence Intervention Components

A taxonomy of 16 mutually exclusive, distinguishable intervention components have been described previously (deBruin et al., 2010) that may be present in a medication adherence intervention.[70] An intervention may be found to include one, several, or all of these components. Examples of these components include features such as knowledge-based activities, awareness-based pursuits, self-efficacy enhancement, and contingent rewards. Our assessment of intervention components was based on whether the studies provided an explicit description of intervention components. Hence, we noted a particular component for a particular intervention only if that component was identifiable from the report. In addition, some studies tested interventions that included components not identified in deBruin's 16-component taxonomy. We included these as "novel components" in our count of the components each study reported and have listed and described them below.

Although the range of the total number of components included in each intervention was somewhat broad (1-9), few interventions involved only one component. Moreover, most interventions with only a single component were not delivered by a specified agent but rather involved a policy or institutional change (such as a reduction in medication copay, novel packaging of pills, or a mailed informational sheet).

The median and modal number of components delivered were both 3: 14 interventions (24 percent) had 3 components, 19 (33 percent) had fewer than 3, and only 3 interventions (5 percent) had more than 6 components. Table 84 shows the reported number of components by agent of delivery. The number of components delivered did not appear to vary greatly based on the agent delivering the interventions. One exception was noted in the case of interventions that were delivered by a multidisciplinary team, which usually had a greater number of components.

Table 84. Reported number of components by delivery agent.

Number of Components	Auto	Multidisciplinary	Nurse	Pharmacist	Physician	Other	Non-specified Agent	Total
1	0	0	0	0	0	2	6	8
2	2	0	0	5	2	1	1	11
3	2	1	1	4	1	4	1	14
4	0	0	3	2	2	0	0	7
5	2	2	0	1	0	1	0	6
6	1	1	1	0	1	1	1	6
7	0	0	2	0	0	0	0	2
8	0	0	0	0	0	0	0	0
9	0	1	0	0	0	0	0	1

The vast majority of the medication adherence interventions reviewed included a knowledge-based component (79 percent). Moreover, about 42 percent of all interventions included an awareness-based component in addition to the knowledge component. The awareness components involved activities to enhance a person's self-awareness, such as awareness of their own health risks, their current health state, or their values and preferences. Examples of activities to raise awareness included risk communication, self-monitoring, reflective listening, and behavioral feedback. Of note, only one intervention involved an awareness-based element without a knowledge-based component.

About half of the interventions (49 percent) used facilitation techniques. Facilitation techniques include the use of supportive activities, such as continuous professional support, helping clients deal with adverse effects, individualizing or simplifying regimens, or reducing environmental barriers to taking medication to improve adherence. Components designed to enhance self-efficacy were included in 13 (32 percent) of the interventions. Activities such as modeling, practicing task-specific skills, verbal persuasion, making plans for coping responses, setting graded tasks, and re-attributing success and failure were coded as self-efficacy enhancements.

Other components that were present in some of the interventions reviewed included intention formation activities (19 percent), action control (18 percent), addressing attitudes (11 percent), motivational interviewing (11 percent), stress management (3.5 percent), and social influence (3.5 percent). Sixteen percent of interventions included a component that addressed maintenance. We identified no interventions that utilized contingent rewards to improve medication adherence in the studies that met our inclusion criteria.

No pattern of the distribution of components was evident among interventions sorted by target. However, as shown in Table 85, a few generalizations about intervention components based on the agent of intervention delivery can be made.

First, all interventions involved knowledge-based components, with the exception of 2 of 9 delivered by nurses and 4 of 9 delivered by other health professionals (such as counselors, health coaches, etc.). However, the pattern of knowledge-based delivery differed for physicians and pharmacists as compared with other agents. When knowledge-based components were delivered by nurses, multidisciplinary teams (those often included nurses), automated systems, and other nonphysician/nonpharmacist health professionals, most (66 percent to 83 percent) were coupled with an awareness-based component that served to raise clients' self-awareness. In contrast, physician and pharmacist-delivered interventions all involved knowledge delivery but were less often coupled with awareness-based elements.

Table 85. Distribution of nine key components most commonly observed in adherence interventions reviewed by agent of delivery

Agent of Delivery	Knowledge, Without Awareness	Knowledge, With Awareness	No Knowledge	Self-Efficacy	Facilitation	Mainte-nance	Inten-tions, Action Control	Inten-tions, Action Control	No Inten-tions, Action Control	No Inten-tions, No Action Control	Moti-vational Intervie-wing	Attitude Changes
Pharmacists (N=12)	8 (67%)	4 (33%)	0	1 (8%)	11 (92%)	2 (17%)	3 (25%)	0	0	9 (75%)	0	0
Physicians (N=6)	4 (67%)	2 (33%)	0	1 (16%)	4 (67%)	0	0	0	0	0	0	0
Nurses (N=9)	1 (11%)	6 (66%)	2 (22%)	5 (55%)	6 (67%)	4 (44%)	2 (22%)	2 (22%)	1 (11%)	4 (44%)	2 (22%)	1 (11%)
Multidisciplinary (N=5)	1 (20%)	4 (80%)	0	2 (40%)	3 (60%)	1 (20%)	1 (20%)	2 (40%)	2 (40%)	0	2 (40%)	0
Automated (N=6)	1 (17%)	5 (83%)	0	3 (50%)	0	1 (17%)	0	0	0	6 (100%)	1 (17%)	2 (34%)
Other health professionals (N=9)	4 (44%)	1 (11%)	4 (44%)	4 (44%)	6 (67%)	0	2 (22%)	0	0	7 (78%)	1 (11%)	2 (22%)

N, number.

Second, physician- and pharmacist-delivered interventions rarely used self-efficacy enhancement components, whereas about half of those delivered by other agent groups used them. No physician interventions addressed maintenance, while nearly half of nurse-delivered interventions (44 percent) did. Finally, none of the automated interventions used facilitation, while nearly all (92 percent) of the pharmacist-delivered interventions did, and about two thirds of each of the other intervention delivery agent groups did.

Similarly, physician and pharmacist-delivered interventions seemed to be less likely to use the components of either intention formation, or action control than nurses and multidisciplinary teams. Only 3 of 18 interventions delivered by physicians or pharmacists included at least one of these two components compared with 10 of 14 interventions delivered by nurses or multidisciplinary teams. No automated interventions involved intention formation or action control.

Motivational-interviewing and attitude-changing components were used less often in general, and neither was ever used by physician or pharmacist-delivered interventions.

Components of Interventions Not Encompassed by deBruin Taxonomy

Some interventions included components that did not appear to fit within deBruin's taxonomy. Because deBruin's taxonomy focuses primarily on individual patient-level components, it is not surprising that many of the novel components we identified targeted systems-level factors. However, we did note two patient-level components that were not included in deBruin's taxonomy: shared decision-making/decision-aid approaches and approaches that specifically tested the effects of "gain-framing" messages. Both components are of interest because they may have an influence on medication adherence and have not received as much focus heretofore. Each of the novel components we identified are listed in Table 86. Shared decision making is distinct from interventions that address self-efficacy. Self-efficacy is a key construct in Social Cognitive Theory that has been used to encourage adoption of health behavior change when there is a clear healthier choice indicated. Self-efficacy is task-specific, and achieved via specified approaches which involves gradual steps. Shared decision-making, in contrast, is not based in psychological theory nor aimed at changing behavior but rather in helping patients decide which health option to choose by providing information and values clarification.

Table 86. Components of interventions not encompassed by deBruin taxonomy

New Components	Level	Target	Agent
Provision of patient adherence data to clinician	Systems	Combination: patient, provider, system	Automated
Shared decisionmaking	Patient	Combination: patient, provider, system	Multidisciplinary
Change on medication cost-sharing with company	Policy	Combination: patient, policy	Company
Reduction of copay/out of pocket expenses	Policy	Policy	NA
Specific packaging design	Systems	Patient	NA or Pharmacist
Gain-framing messages	Patient	Patient	Nurse
Pharmacist-physician collaboration	System	Patient, provider, system	Pharmacist
Monitoring of medication regimen to identify system errors	System	Patient, system	Pharmacist
Appointment making for patients	System	Combination: patient, system	Pharmacist
Collaborative care between physicians	System	Combination: Patient, Provider, system	Physician

NA, not applicable.

Key Question 3b. Direct Comparisons of Intervention Characteristics and Medication Adherence Outcomes

Description of Studies

Overview

We found four articles comprising only three randomized trials (5 percent) that assessed the effects of four different interventions aimed at improving medication adherence among adult patients; one involved patients with heart failure, two involved patients with asthma, and one involved patients with diabetes mellitus.[86, 87, 110, 121, 122] Table 87 presents an overview of the interventions. Table 88 through Table 92 present results for medication adherence and other outcomes for all three studies, followed by strength-of-evidence tables by type of intervention (Table 93 through Table 95). KQ 1 presents complete results for outcomes for all comparators, including controls; the tables in this section focus on direct comparisons only. We rated all of these studies as having medium risk of bias.[86, 110, 122].

Population

All three studies were conducted among adults. The study of diabetes patients reported limiting the sample to patients with type 2 diabetes or who were on oral hypoglycemic agents. [86, 87] One study was restricted to poorly controlled asthma.[122] In the study of heart failure, all participants were restricted to those older than 65 years, with African-American participants comprising between 23 to 33 percent.[110]

Interventions

Interventions varied widely in their approaches to improving adherence, although all were directed at patients (Table 87).

The asthma studies focused on providers and systems in addition to patients.[122] They evaluated shared decisionmaking between patients and clinicians.[122]

Both the diabetes and heart failure studies were directed solely at patients.[86, 87, 110] The heart failure study included two intervention arms and one control arm.[110] The diabetes study evaluated the effects of a lipid-lowering decision aid while directly comparing the effect of the agent of delivery (clinician or researcher).[86, 87] In the heart failure study, adherence reminder calls were delivered via video using provided equipment to the first intervention arm and via telephone calls to the second intervention arm; a research assistant reminded participants to take their medications daily.[110]

Comparator

For KQ 3, the relevant comparator was a modification of the intervention. In the asthma study[122] for example, shared decisionmaking was compared with clinical decisionmaking (and both were compared with a control condition). In the study of statin decision aids among patients with diabetes, patients were compared regarding whether the intervention was delivered by a physician or research staff member.[86, 87] In the study of video and phone call reminders, these two approaches were compared with each other (as well as a control group) among patients with heart failure and no calls were made to the control group.[110]

Outcome and Timing

The asthma study defined percentage adherence as the number of doses taken divided by the number prescribed and used metered dose inhaler data, pharmacy refill data, or a combination of self-reported adherence and electronic monitoring data to construct the measure, depending on what was available but generally using objective measures for the numerator. The investigators also evaluated refills of short-acting beta-agonists (SABA) using refill data.[122]

The study of diabetes patients used a single self-report item to ask about medication taking using a 7-day recall period[86] to count the number of people who missed no doses.[86] The congestive heart failure studies measured adherence via Medication Event Monitoring System (MEMS) caps.[110]

The study of a lipid-lowering decision aid for diabetic patients did not evaluate the effect of the intervention on biomarkers, but the asthma study assessed the effects of a shared decision-making intervention effects on forced expiratory volume (FEV-1).[122] Other outcomes of interest included the Asthma Therapy Assessment Questionnaire (ATAQ) and health-related quality of life.[122]

Timing and frequency of the study outcomes assessments varied, ranging from 6 weeks to 2-year followup, as did the timing of the outcome assessment relative to administration or completion of the intervention. For example, the shared decision-making study recorded 2-year adherence information for an intervention with an active component that lasted 9 months.[122] The diabetes intervention was administered in one contact at baseline, and followup occurred 6 weeks later. The heart failure study assessed adherence outcomes at the conclusion of the intervention,[110] which lasted 6 weeks.

Setting

The asthma study worked within health systems.[122] The diabetes study recruited from a metabolic specialty clinic where the intervention was also delivered.[86, 87] The heart failure study focused on a population recruited from an urban home health agency and ambulatory care clinic[110] but delivered the intervention in patients' homes.[110]

Applicability

For each intervention type, the scarcity of evidence limits the statements we can make about the applicability of the findings to subpopulations along the spectrum of severity and in different settings. The most significant limitation to applicability in the diabetes study is the lack of long-term outcome data. Notable limitations to applicability in the heart failure study included the low participation rate (10 percent) among those eligible.[110]

Key Points

Overview

- All three studies assessed intervention effects on medication adherence (e.g., percentage of patients achieving a threshold of pills taken, proportion of pills taken, etc.) albeit each used a slightly different definition of medication adherence and tested different interventions.
- Only one of three studies demonstrated a statistically significantly effect for direct comparisons of specific intervention components on improving medication adherence.

Shared Decisionmaking Compared with Clinical Decisionmaking

- Shared decisionmaking resulted in improved medication adherence within the first year of initiating treatment when compared with clinical decisionmaking (low strength of evidence).
- Biomarkers for shared decision-making interventions: Shared decisionmaking resulted in improved pulmonary function within the first year of initiating treatment when compared with clinical decisionmaking (low strength of evidence).
- Morbidity: We found no statistically significant differences in symptom improvement for shared decision-making interventions when compared with clinical decisionmaking (insufficient evidence).
- Health care utilization and quality of life for shared decision-making interventions: We found no difference between two intervention groups in reduced asthma-related visits or mini-asthma quality-of-life scores within the first year of initiating treatment (low strength of evidence).

Decision Aid Delivered by Clinician Compared with Research Staff

- Medication adherence: There is no evidence that improved medication adherence among patients with diabetes and comorbid depression was influenced by agent of delivery (insufficient).

Adherence Reminders Delivered by Video Compared with Telephone

- Medication Adherence: Evidence from a single, small study with limited followup suggests that there was no evidence of difference between mode of delivery. (insufficient)

Other Outcomes

- All other outcomes for the interventions listed above: Insufficient due to lack of evidence.

Detailed Synthesis for Shared Decisionmaking

Medication Adherence

The asthma trial that evaluated shared decisionmaking and clinical decisionmaking compared with usual care found statistically significant differences in medication adherence at 1-year followup; clinical decisionmaking was more effective than usual care, and shared decisionmaking was more effective than either clinical decisionmaking or usual care, suggesting evidence of benefit for shared decisionmaking (Table 93).[122] At 2 years, clinical decisionmaking was no longer significantly different than usual care, but shared decisionmaking continued to produce statistically significant improvements in medication adherence compared with clinical decisionmaking or usual care.

Other Outcomes

One trial reported no significant difference in improved pulmonary function for the shared decision-making group compared with the clinical decision-making group (Table 89).[122] Although both intervention arms had a higher odds of reporting no asthma control problems and lower acquisition of short-acting beta agonists ([SABA] total days supply acquired in a year/365 days) compared with usual care at 1 year, no statistically significant difference was found

between the two arms for these two morbidity outcomes (Table 90). Similarly, at 2 years, although only the shared decision-making arm reported lower SABA use than usual care, no statistically significant difference existed between the two intervention arms in this regard (Table 90). No differences between clinical- and shared decision-making arms were found for quality of life (Table 91) or asthma-related visits (Table 92).

Detailed Synthesis for Decision Aids

Medication Adherence

The decision-aid intervention increased the number of people who missed no doses in the last week compared with controls but no difference was found based on who delivered the aid (Table 88), suggesting insufficient strength of evidence (Table 94). This same study also assessed medication persistence (the proportion of patients still on treatment at followup) but found no difference between the groups.[86]

Detailed Synthesis for Video and Telephone Reminders

Medication Adherence

Although the congestive heart failure study showed statistically significant improvement in at least one measure of medication adherence in the intervention group compared to the control group,[110] the difference between the two intervention groups, which differed by mode of delivery, was not statistically significant (Table 88), resulting in insufficient strength of evidence (Table 95).

Table 87. Medication adherence interventions with direct comparisons: study characteristics

Author, Year N at Randomization	Population Setting	Intervention and Comparator
Fulmer et al., 1999[110] N=60	Adults ≥65 years old with a diagnosis of heart failure; use of an ACE inhibitor, calcium channel blocker, or beta-blocker Urban home health care agency and ambulatory care clinic	G1: For 6 weeks, participants received video reminder calls to take their medications daily (Monday through Friday). The call consisted of a brief greeting and a question about whether the previous day's medication had been taken, and additional time to answer patients' questions G2: This group received the same intervention as G1, but via regular phone call with no video component G3: Received no reminder calls (control)
Weymiller et al., 2007[86] Jones et al., 2009[87] N=98	Adults with type 2 diabetes mellitus Metabolic specialty clinic at Mayo Clinic	G1: Statin choice decision aid G1a: Delivered by research staff before medical visit G1b: Delivered by clinician during medical visit G2: Standard of care educational pamphlet control G2a: Delivered by research staff before medical visit G2b: Delivered by clinician during medical visit
Wilson et al., 2010[122] N=612	Adults ages 18 to 70 Kaiser Permanente medical centers	G1: Shared decision-making model for two face-to-face visits and three phone calls G2: Clinical decision-making model for two face-to-face visits and three phone calls G3: Usual care: stepped approach to medications (control)

Abbreviations: ACE, angiotensin-converting enzyme; G, group; N, number.

Table 88. Medication adherence interventions with direct comparisons: medication adherence outcomes

Study N Analyzed for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
Fulmer et al., 1999[110] G1: 17 G2: 15 G3: 18	Compliance rates monitored during a 2-week pre-intervention phase (baseline), 6-week intervention phase (time 2), and 2-week postintervention phase (time 3); MEMS/Nonself-report	Average compliance rates Baseline: G1: 82% G2: 76% Time 3: G1: 84% G2: 74% 95% CI, NR p: There was a statistically significant time effect during the course of the study from baseline to postintervention (F=4.08, p<0.05) in which G1 and G2 showed enhanced compliance relative to the control. However, there was no significant difference between compliance in G1 and G2.
Weymiller et al., 2007[86] Jones et al., 2009[87] *G1: 33 *G2: 29 *number on statins at follow-up G1a: NR G1b: NR G2a: NR G2b: NR	Number of people who missed no doses in the last week 3 months after receiving the intervention by mode of delivery	G1a: NR G1b: NR G2a: NR G2b: NR OR for mode of delivery: 0.8 95% CI, 0.3, 2.6 p:NS
Wilson et al., 2010[122] G1: 204 G2: 204	Medication acquisition ratio for all asthma medications (total days supply acquired in a year/365 days) Pharmacy refill data/Nonself-report	Means at 1 year: G1: 0.67 G2: 0.59 (95% CIs): G1-G2: (0.01 to 0.15), p =0.0029 Mean differences at 2 years: G1-G2: 0.04 (95% CIs): G1-G2: (-0.04 to 0.12)
	Medication acquisition ratio for inhaled corticosteroids (total days supply acquired in a year 365 days) Pharmacy refill data/Nonself-report	Means at 1 year G1: 0.59 G2: 0.52 (95% CIs):NR p:G1-G2, 0.017
	Acquisition of beclomethasone canister equivalents Pharmacy refill data/Nonself-report	Means at year 1: G1: 10.9 G2: 9.1 (95% CIs): G1-G2: (0.57 to 0.31), p=0.005 Means at year 2: G1: 7.1 G2: 5.8 (95% CIs): G1-G2: (0.04 to 2.7), p=0.04

Table 88. Medication adherence interventions with direct comparisons: medication adherence outcomes (continued)

Study N Analyzed for Each Group	Adherence Measure Source/Method	Outcomes for Each Time Point
Year 1: G1: 40 G2: 44 Year 2: G1: 112 G2: 108	Medication acquisition for long-acting beta-agonists Pharmacy refill data/Nonself-report	Mean difference at 1 year: G1-G2: 0.09 (95% CIs): G1-G2: (0.02 to 0.17) Mean difference at 2 years: G1:G2: 0.09 (95% CIs): G1-G2: (0.01 to 0.18)

Note: comparisons with usual care are not presented in this table.

Abbreviations: CI, confidence interval; G, group; MEMS, Medication Event Monitoring System; NR, not reported; NS, not significant; OR, odds ratio.

Table 89. Medication adherence interventions with direct comparisons: biomarkers

Author, Year N in Each Group	Outcome Source/Method	Results
Wilson et al., 2010 [122] G1: 182 G2: 180	FEV1% Spirometry	Means at 1 year: G1: 76.5% G2: 75.8% (95% CIs): G1-G2: (NR), p=0.47
	FEV1:FEV6 ratio Spirometry	Means at 1 year: G1: 72.8% G2: 71.8% (95% CIs): G1-G2: (NR), p =0.09

Abbreviations: CI, confidence interval; G, group; FEV, forced expiratory volume; NR, not reported

Table 90. Medication adherence interventions with direct comparisons: morbidity

Author, Year N in Each Group	Outcome Source/Method	Results
Wilson et al., 2010 [122] G1: 182 G2: 180	Asthma control in previous 4 weeks ATAQ 4 items; Range NR (lower score=better)	Mean change in ATAQ score at 1 year G1: -0.80 G2: -0.54 95% CI, NR p: NR
G1: 204 G2: 204	Mean equivalents of SABA acquired Pharmacy refill data	Means in Year 1: G1: 6.5 G2: 7.1 G1-G2: p=0.09 95% CI, NR Means in Year 2: G1: 4.7 G2: 6.0 G1-G2: p=0.06 95% CI, NR

Abbreviations: ATAQ, Asthma Therapy Assessment Questionnaire; CI, confidence interval; G, group; NR, not reported; OR, odds ratio; SABA, short-acting beta-agonists; SD, standard deviation.

Table 91. Medication adherence interventions with direct comparisons: quality of life

Author, Year N in Each Group	Outcome Source/Method	Results
Wilson et al., 2010[122] G1: 182 G2: 180	Quality of Life Symptom Subscale of the MAQLQ 5 items; Range NR (higher score=better)	Mean symptom subscale scores at year 1 G1: 5.5 G2: 5.4 95% CI, NR G1-G2: p>0.05

Abbreviations: CI, confidence interval; G, group; MAQLQ, Mini Asthma Quality of Life Questionnaire, NR, not reported.

Table 92. Medication adherence interventions with direct comparisons: healthcare utilization

Author, Year N in Each Group	Outcome Source/Method	Results
Wilson et al., 2010 [122] G1: 204 G2: 204	Number of asthma-related visits per year Electronic medical records	Means at 1 year postrandomization: G1: 1.0 G2: 1.1 (95% CI): G1-G2: (-0.29 to 0.30), p=0.97

Abbreviations: CI, confidence interval; G, group.

Table 93. Asthma: strength of evidence for shared decision-making interventions

Intervention	Number of Studies; Subjects (Analyzed)*	Outcome	Study Design/ Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Shared decision making vs. clinical decisionmaking	1; 612 (612)	Medication adherence	RCT Medium	Unknown	Direct	Precise	Difference in medication acquisition ratio at 1 and 2 years for all asthma medications except beclamethasone: 0.04 to 0.09 (range) Low SOE of benefit Difference in medication acquisition ratio at 1 and 2 years for beclamethasone: 1.3 to 1.8 (range) Low SOE of benefit
	0	Mortality	NA	NA	NA	NA	Insufficient
	1; 612 (551)	Pulmonary function	RCT Medium	Unknown	Direct	Precise	Difference in FEV1 percentage points: 0.7 to 1.0 Low SOE of benefit
	0	Inflammation markers	NA	NA	NA	NA	Insufficient
	1; 612 (612)	Symptom improvement	RCT Medium	Unknown	Direct	Precise	Insufficient
	1; 612 (551)	Quality of life	RCT Medium	Unknown	Direct	Precise	Difference in subscale scores on 5-item MAQLQ: 0.1 Low SOE of no benefit
	0	Patient satisfaction	NA	NA	NA	NA	Insufficient
	0	Quality of care	NA	NA	NA	NA	Insufficient
	1; 612 (612)	Healthcare utilization	NA	Unknown	Direct	Precise	Difference of 0,1 fewer asthma-related visits per year Low SOE of no benefit

Abbreviations: FEV1, forced expiratory volume in one second; MAQLQ, Mini Asthma Quality of Life Questionnaire; NA, not applicable; RCT, randomized controlled trial; SABA, short-acting beta-agonists; SOE, strength of evidence.

Table 94. Decision aids for diabetes: strength of evidence

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Study Design/ Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Statin decision aid vs. standard written information about lipids	1; 98 (NR)	Medication Adherence	RCT Medium	NA	Direct	Precise	Insufficient

Abbreviations: NA, not applicable; NR, not reported; RCT, randomized controlled trial.

Table 95. Heart failure: strength of evidence for reminders delivered by video and telephone

Intervention	Number of Studies; Subjects (Analyzed)*	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Heart Failure: Video and telephone reminders	1; 60 (50)	Medication Adherence	RCT Medium	Unknown (sig improved)	Indirect	Imprecise	Insufficient
	0	Mortality	NA	NA	NA	NA	Insufficient
	0	Biomarkers	NA	NA	NA	NA	Insufficient
	0	Health care Utilization	NA	NA	NA	NA	Insufficient
	0	Quality of care	NA	NA	NA	NA	Insufficient
	0	Patient satisfaction	NA	NA	NA	NA	Insufficient

Abbreviations: NA, not applicable; RCT, randomized controlled trial.

Key Question 4. Vulnerable Populations

Description of Included Studies

Overview

We found 12 studies that attempted to improve medication adherence in vulnerable populations.[74, 83, 84, 97, 109, 110, 112, 129-131, 133, 148] We present population, intervention, comparator, outcome and timing, and setting below, followed by key points and a detailed discussion for each vulnerable population. Because KQ 1 presents detailed results for all studies, this section presents only strength of evidence grades.

Population

Vulnerable populations of interest to our review included but were not limited to the following: racial and ethnic minorities; populations with special health care needs (such as low health literacy; coexisting conditions; persistent or severe disease); the elderly; and low-income, underinsured or uninsured, and inner-city or rural populations. We considered studies as including elderly populations if the subjects were 65 years of age or older. In nine of these 12 studies, the study was conducted entirely in the vulnerable population; that is, the vulnerable population was not a subgroup but comprised the entire study sample[74, 83, 84, 97, 109, 110, 112, 133, 148] In the remaining three studies, the vulnerable populations were subgroups within the overall study sample;[129-131] two studies conducted subgroup analyses based on major depression[129, 130] and one study focused on moderate- to high-severity depression.[131]

Among the nine studies in which the entire study was conducted in vulnerable groups, the various populations differed. In five studies, the vulnerable populations were the elderly; of

these, four defined the elderly as those who were ages 65 or older,[74, 109, 110, 148] and one defined elderly as those who were greater than 70 years old.[112] In four studies, the vulnerable population involved patients with depression. Of these, two involved patients with depression and diabetes,[83, 84] one included patients with depression and HIV;[133] and one focused on patients with depression and hypertension.[97] One of the studies that examined coexisting conditions also included African American primary care patients.[84]

Intervention

Eight studies involved systems changes. Of these, six examined some form of collaborative care or multifaceted interventions involving patient interaction with multiple types of health care providers.[83, 112, 129-131, 133] One study examined a collaborative care model with HIV and mental health clinicians;[133] three others examined collaborative care provided by a primary care physician and a psychologist and psychiatrist;[129-131] one tested a multidisciplinary intervention that included teaching by a study team, the involvement of a nurse, registered dietician, social services representative, and a geriatric cardiologist;[112] and one described an individualized management of depression that involved psychiatric consultations and group services among other features.[83]

The same team conducted two integrated care interventions that dealt with patients with depression.[84, 97] The studies were identical except for the comorbid condition on which the study focused: diabetes[84] or hypertension.[97] In addition to telephone calls and care coordination, the care management interventions in these studies also included multiple in-person visits.

Three other studies focused primarily on the patient.[74, 109, 110] In one, patients in the intervention group received medication in a daily-dose adherence blister package that had information on what to do if a dose was not taken.[109] Another study had a prospective observational phase with three distinct elements: medication education, usage of blister packs as an adherence aid, and followup with clinical pharmacists.[74] After this initial phase was completed, meetings with pharmacists continued as did the use of medication aids, but the medication education continued only on an as-needed basis.[74] A third study used a video reminder call for one group of patients and a telephone reminder call (without video) for the second group.[110]

Finally, a single study focused on policy change, specifically, the impact of Medicare Part D prescription drug coverage on medication adherence.[148]

Comparator

All studies compared the active intervention with usual care or control group populations.[74, 83, 84, 97, 109, 110, 112, 129-131, 133, 148] In certain studies where the intervention focused on collaborative care, usual care was described as involving depression care by primary care physicians, which included antidepressants and referrals to specialty mental health services on an as-needed basis.[83, 129-133] In one study, patients in the usual care group received conventional care from a physician without the collaborative care process that the intervention group received.[112] In the two integrated care studies, usual care was described generally as routine care appropriate to the setting.[84, 97] In one study in which the intervention group received blister-packaged medication, the usual care group received traditional bottles of medication.[109] Similarly, in a study that combined education, pharmacist followup, and adherence aid use in the intervention, the usual care group did not receive medication education or blister-packaged medication.[74] In another study, the comparator group did not receive the reminder calls that the intervention groups

received.[110] In the only study focusing on policy change, the comparator for the Medicare Part D intervention groups was described as retiree health benefits with no deductible but copayments for each monthly prescription.[148]

Outcome and Timing

All studies reported on medication adherence for the relevant vulnerable population described, either as a subgroup analysis or as the overall main analysis in nine studies in which the entire study sample comprised a vulnerable population.[74, 83, 84, 97, 109, 110, 112, 129-131, 133, 148] However, medication adherence outcomes varied markedly across the studies; some studies reported multiple outcomes. The types of medication adherence outcomes reported included measures of adherence using thresholds of 80 percent or greater[74, 84, 97, 133] and 95 percent or greater.[133] Other types of medication adherence outcomes included medication possession ratios (MPRs),[109, 148] adherence to adequate dosage from pharmacy refill data,[131] self-reported medication adherence,[130] percentage of patients receiving adequate dosage of medication,[129] percentage of patients who had prescription filled on time,[109] percentage of patients who were adherent in specified time frames,[74] and percentage of prescribed doses taken using the medication event monitoring system (MEMS).[110]

Most studies reported on medication adherence outcomes during the intervention period or immediately following it or within a period after the conclusion of the intervention that ranged from a few weeks to 12 months[83, 84, 97, 109, 112, 129, 130, 133] In one study, adherence was monitored during a 2-week pre-intervention phase in addition to taking measurements at the end of the study and 2 weeks following the end of the study.[110] One study reported on long-term outcomes up to 28 months after initial randomization was complete.[131] One study, which was 14 months with an initial 2-month run-in period followed by a 6-month cohort intervention, ended with a final 6-month randomized controlled trial (RCT).[74] In this particular study, outcomes obtained at 14 months were considered to be 6-month outcomes for the RCT portion.[74] In the only study in the set focused on policy change, MPRs were tracked for 2 years before and 2 years after the introduction of Medicare Part D in four different groups.[148]

Setting

Two integrated care studies were set in community-based primary care clinics.[84, 97] Several collaborative care studies were set within primary care clinics in the Group Health Cooperative in Washington State.[83, 129-131] One collaborative care study was conducted in a university teaching hospital[112] and another was set in a Veterans' Administration (VA) HIV clinic.[133] The blister-packaging study was set in ambulatory care clinics in Columbus, Ohio, and Tucson, Arizona.[109] Another study was set in a university-affiliated tertiary care U.S. military medical center.[74] The video-reminder study recruited patients from a large urban home health agency and an urban ambulatory clinic, with the intervention delivered via telephone calls.[110] The policy change study was conducted by examining administrative data of patients enrolled in a large insurer's Medicare Advantage products.[148]

Key Points

- We found varying strength of evidence regarding interventions to improve medication adherence among vulnerable populations. Interventions aimed at improving medication adherence generally had a positive impact for most vulnerable populations for which we

found evidence, improving adherence in all but two populations considered. The interventions, the diseases being treated, and the methods for measuring medication adherence outcomes differed considerably across studies.

- Evidence of improved medication adherence was seen for the following: patients with major depression, severe depression, multiple chronic conditions, or depression with hypertension comorbidity; African American patients with depression and diabetes; and elderly patients with diabetes, hyperlipidemia, congestive heart failure, or hypertension (low strength of evidence).
- No evidence of improvement in medication adherence was seen for patients with depression and HIV or for patients with diabetes and depression (insufficient evidence).
- No evidence was available for the following: racial and ethnic minorities with the exception of those who identified as African American race; populations with certain specific special health needs such as low literacy, low-income populations, and underinsured and uninsured populations (insufficient evidence).

Detailed Synthesis

The following synthesis lists results for vulnerable populations by clinical condition. Table 96 presents strength of evidence grades.

Diabetes

Among elderly patients with diabetes, Medicare Part D improved adherence to medications for prevention of cardiovascular issues. This effect was much greater among those who had no prior insurance coverage before Medicare Part D than for those who did have some prior coverage.[148]

Diabetes and Depression

Among patients with diabetes who suffered from depression, a collaborative intervention did not improve medication adherence to angiotensin converting enzyme (ACE)-inhibitors, oral hypoglycemic agents, and lipid-lowering agents.[83]

Hyperlipidemia

Among elderly patients with hyperlipidemia, Medicare Part D improved adherence to lipid-lowering medications. This effect was much greater among those who had no prior insurance coverage before Medicare Part D than for those who did have some prior coverage.[148]

Hypertension

Among elderly patients with hypertension, an intervention involving daily-dose blister packaging improved adherence.[109]

Congestive Heart Failure

A video-or telephone-based intervention improved medication adherence among elderly patients with congestive heart failure when compared with a usual care control group[110] A multidisciplinary intervention also improved medication adherence outcomes among elderly patients with congestive heart failure.[112]

Depression

Major Depression

One study demonstrated statistically significant improvement in medication adherence compared with usual care for both subgroups of major and minor depression at 7 months after randomization.[129] Another study found significantly improved medication adherence in the intervention arm compared with the control arm at 4 and 7 months after randomization for major and minor depression groups for percentage adherent, with the exception of the 7-month followup for major depression.[130]

Severe Depression

In one study, adherence outcomes were recorded during 6 month intervals through 30 months after randomization; overall differences were observed by intervention arms at 3 and 6 months after randomization.[131] Among patients who were severely depressed at baseline, the intervention arm continued to show benefits of the intervention on medication adherence at 12 months.[131]

Depression and Diabetes

Among African American patients with depression and diabetes condition, an integrated care intervention improved adherence to medications for both diabetes and depression.[84]

Depression and Hypertension

Among patients ages 50 years or older with depression and hypertension, an integrated care intervention improved adherence to medications for both hypertension and depression.[97]

Depression and HIV

A multifaceted collaborative care intervention did not significantly improve medication adherence for either antidepressants or HIV medication adherence for patients who were depressed and had an HIV diagnosis.[133]

Multiple Chronic Conditions

One study showed that among elderly patients taking at least four medications for chronic diseases, a pharmacy care program resulted in significant improvements in medication adherence.[74]

Table 96. Vulnerable populations: strength of evidence

Intervention Vulnerable Population	Number of Studies; Subjects (Analyzed)	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence Magnitude of Effect (G1 – G2)
Medicare Part D Elderly patients with diabetes or hyperlipidemia	1; 20,889[148]	Before-after study Medium	Unknown	Direct	Precise	Varied measures and magnitude Low
Collaborative intervention Diabetes patients with depression	1; 329[83]	RCT Medium	Unknown	Direct	Imprecise	Insufficient
Blister packaging Elderly patients with hypertension	1; 85[109]	RCT Low	Unknown	Direct	Precise	Difference in percentage points for patients who refilled prescriptions on time: 14.3 Difference in medication possession ratio: 0.06 Low
Video- or telephone-based intervention Elderly patients with congestive heart failure	1; 50[110]	RCT Medium	Unknown	Direct	Precise	Difference in percentage points for prescribed medication doses taken: 27 for video-telephone reminder group; 17 for telephone reminder group Low
Multidisciplinary intervention: collaborative care Elderly patients with congestive heart failure	1; 156[112]	RCT Medium	Unknown	Direct	Precise	Varied measures and magnitude Low
Multidisciplinary intervention: collaborative care Patients with major depression	2:[129, 130]	RCT Medium	Consistent	Direct	Precise	Varied measures and magnitude Low
Multidisciplinary intervention: collaborative care Patients with severe depression	1;[131] 6 months: 229 28 months: 187	RCT Medium	Unknown	Direct	Precise	Varied measures and magnitude Low

Table 96. Vulnerable populations: strength of evidence (continued)

Intervention Vulnerable Population	Number of Studies; Subjects (Analyzed)	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence Magnitude of Effect (G1 – G2)
Integrated care Patients with depression with hypertension	1; 64[97]	RCT Medium	Unknown	Direct	Precise	Difference in percentage points for adherence to depression medication: 40.6 Difference in percentage points for adherence to hypertension medication: 10 Low
Integrated care African American patients with depression and diabetes	1; 58[84]	RCT Medium	Unknown	Direct	Precise	Difference in percentage points of patients with greater than or equal to 80% adherence to hypoglycemic agent: 13.8 Difference in percentage points of patients with greater than or equal to 80% adherence to an antidepressant: 13.8 Low
Collaborative care Depression and HIV	1; 249[133]	RCT Medium	Unknown	Direct	Imprecise	Insufficient
Pharmacy care program Patients with multiple chronic conditions	1; 159[74]	RCT Medium	Unknown	Direct	Precise	Difference in percentage points in medication adherence: 26.4 Difference in percentage points of patients with greater than or equal to 80% adherence to all medications: 75.7 Low

G, group; RCT, randomized controlled trial.

Key Question 5. Harms

Description of Included Studies

Three randomized control trials addressed unintended consequences, or harms, associated with interventions to improve medication adherence (Table 97).[92, 103, 111]

Table 97. Harms: trial characteristics

Author, Year N at Randomization	Population Setting	Intervention and Comparator
Carter et al., 2009[103] N=402	Adults >21 years diagnosed with hypertension Community-based family medicine residency programs	G1: Physician/pharmacist collaborative model in which pharmacists addressed suboptimal medication regimens and poor medication adherence and gave feedback to physicians. Study nurses also gave patients educational information and encouraged lifestyle modifications. G2: Patients received blood pressure measurements at baseline, 3 and, 6 months and educational information from nurses. Clinical pharmacists abstained from providing care to patients in control group.
Murray et al., 2007[111] N=314	Adults ≥ 50 years of age with heart failure University-affiliated ambulatory care practice	G1: Pharmacist-led intervention providing verbal instructions, literacy-sensitive written materials, and labeling of medications with icons to promote medication adherence G2: No contact with intervention pharmacist other than initial medication history
Schectman et al., 1994[92] N=102 (Niacin) N=62 (Bile acid sequestrant)	Adults with hyperlipidemia requiring treatment with either niacin or a bile acid sequestrant Veterans Affairs medical center	G1: Following initial clinic visit, received 5 calls over 28 days from a certified medical assistant to address problems and adverse events associated with medications; when needed, additional telephone contact arranged with physician or clinical pharmacist G2: No telephone contact following initial clinic visit

Population

One trial included adults older than 21 years of age who had been diagnosed with essential hypertension, were taking zero to three antihypertensive medications, did not have diabetes, and had systolic blood pressure (SBP) values or diastolic blood pressure (DBP) values within specific ranges (SBP, 140-179 mm Hg; DBP, 90-109 mm Hg).[103] It also included hypertensive patients who had diabetes if their SBP was between 130-179 mm Hg or DBP between 90-109 mm Hg.[103] Another trial included patients ages 50 years or older who had a confirmed diagnosis of heart failure.[111] Furthermore, participants had to receive all their care at Wishard Health services, regularly have used at least one specified medication for heart failure, and not have plans to use a medication adherence aid. In the third trial, participants were patients with hyperlipidemia who required treatment with either niacin or bile acid sequestrant (BAS) therapy but had not taken either before.[92]

Intervention

One trial evaluated a collaborative model including care from a physician and a pharmacist.[103] In another trial the intervention was pharmacist-led.[111] In the third trial, the intervention was based on telephone contact made to patients by trained health care professionals.[92]

Comparator

In the trial using the collaborative model, the comparison group received no clinical pharmacist intervention.[103] In the pharmacist-led trial, the control group comparison was also the absence of clinical pharmacist intervention but the patients received usual care.[111] Usual care was defined as receiving prescriptions from pharmacists who did not have specialized training from a

multidisciplinary team and did not have access to patient-centered study materials.[111] In the telephone-based trial, the comparison group received no telephone intervention.[92]

Outcome and Timing

All trials presented various medication adherence outcomes. For KQ 5, we focused on outcomes related to side effects, harms, and unintended consequences. In the collaborative model trial, patients provided information on a 47-item questionnaire. This questionnaire, developed and used originally in a previous study, was administered here by trial nurses, on symptoms that were suggestive of adverse events.[103, 150] This questionnaire was administered at baseline and again at 6-month followup. In this questionnaire, each subject was asked, "In the past 4 weeks, how much have you been bothered by…" for every potential reaction. Subjects could respond with one of the following responses, and the scores for these responses were summed (with a total score range of 0 – 188): *not at all* (score: 0); a little bit (score: 1); *somewhat* (score: 2); *quite a bit* (score: 3) or *very much* (score: 4).[150] The resulting symptom score, which was a sum of the score for each item on potential reactions, is thought to be indicative of adverse events. This measured was conducted once at baseline and once at the 6-month followup. In the pharmacy-ambulatory care practice trial, the investigators measured the number of adverse events or medication errors using a program that identified adverse events from the medical record system.[111] They did not indicate the exact timing of these measurements.[111] In the Veterans Affairs (VA) trial, patients reported adverse events associated with medications to clinic staff. Although the investigators collected these self-reported data at 2, 4, and 6 months after randomization, they reported results for only the 2-month point.[92]

Setting

The trials were conducted in various settings: community-based family medicine residency programs,[103] a university-affiliated ambulatory care practice,[111] and a VA lipid clinic.[92]

Key Points

- In the collaborative model trial, the symptom score, which was indicative of adverse events, decreased for both the intervention and control groups.[103] In the other two trials included here, the number of adverse events in the intervention group did not differ significantly from the control group. In the ambulatory practice trial, adverse events included frequently occurring events such as cough or allergy related to angiotensin-converting enzyme (ACE) inhibitors; they also included, serum digoxin concentrations at toxic levels, and use of nonsteroidal anti-inflammatory medications in patients with either high serum potassium or renal insufficiency. Finally, in the VA trial, adverse events included frequently reported effects upon receiving niacin or BAS; these were specifically flushing, pruritus, rash and heartburn (for patients receiving niacin) and constipation, bloating, flatulence, and heartburn (for patients receiving BAS).[92]
- The results offer no evidence of greater adverse events in the intervention than in the comparison groups. Because of the differences in the kinds of adverse events assessed in these three studies, in the interventions, and in the diseases and medications, the evidence is insufficient to draw any conclusions about unintended consequences associated with interventions to improve medication adherence.

Detailed Synthesis

In two trials medication adherence did not improve with the intervention[92, 103] (Table 98). In the ambulatory care practice trial, medication adherence improved during the 9-month intervention period, but this result was not seen in the 3-month poststudy period.[111] In two of the three studies, the intervention group did not have a significantly different number of adverse events from the control group.[92, 111] In the collaborative model trial, medication use (but not medication adherence) increased for both the control and the intervention groups, but the symptom score decreased in both groups; differences in the intervention group from 6 months to baseline were statistically significant, as were differences between control and intervention groups at 6 months.[103] Therefore, among the three trials included, the number of adverse events did not differ between the intervention arms and the control arms;[92, 111]in one case, the difference in adverse events favored the intervention arm.[103]

Table 98. Harms: adverse events outcomes

Author, Year N Analyzed	Adverse Event Outcome	Timing of Adverse Event Measurement and Data Source	Results
Carter et al., 2009[103] G1: 192 G2: 210	Mean total adverse event score	Measured twice, once at baseline and once at 6-month followup Adverse event questionnaire with 47 items, developed for another study and administered by study nurses	Baseline: Mean (SD) G1: 28.0 (23.0) G2: 42.1 (24.2) 95% CI, NR p<0.001 6-month followup (Mean (SD)) G1: 16.6 (12.5) G2: 39.2 (24.2) 95% CI, NR p<0.001 Between-group difference at 6 months p<0.001. However, this does not adjust for difference at baseline.
Murray et al., 2007[111] G1: 112 G2: 192	Number of adverse drug events or medication errors	NR Measured using a program that identified adverse events from the medical record system	G1: 42 (37.5%) G2: 91 (47.4%) 95% CI, NR p: 0.094
Schectman et al., 1994[92] Niacin: G1: 40 G2: 40 BAS: G1: 18 G2: 20	Percentage of patients reporting adverse events associated with medications at 2 months	2 months; measured at 2, 4, and 6 months; only 2-month results reported Self-report to clinic staff	Niacin: flushing, pruritis, rash, heartburn (%) G1: 70, 32, 15, 9 G2: 63, 29, 12, 5 95%CI: NR p: NS, no number given BAS: constipation, bloating, flatulence, heartburn (%) G1: 44, 23, 19, 15 G2: 26, 22, 11, 11 95% CI, NR p: NS, no number given

Abbreviations: BAS: bile acid sequestrant therapy; G: group; NR: not reported; NS: not significant.

Discussion

This section summarizes key findings and strength of evidence for each key question (KQ), followed by a summary of the limitations of the review, limitations of the evidence base, gaps in the evidence that may benefit from future research, and overall conclusions.

Key Findings and Strength of Evidence

Key Question 1. Effect of Patient, Provider, or Systems Interventions on Medication Adherence and Other Outcomes

Overview

Overall, the evidence from 54 studies suggests that numerous pathways provide opportunities to improve medication adherence across clinical conditions (Appendix G). These include relatively low-cost, low-intensity telephone and mail interventions. They also include some relatively intense interventions, such as care coordination and case management (requiring close and ongoing monitoring of patients) and collaborative care (requiring a restructuring of typical U.S.-based health care delivery). Despite evidence suggesting that several interventions offer promising approaches to improving medication adherence, evidence exists for only a subset of these effective interventions showing that the improved adherence is accompanied by improvements in other outcomes, such as biomarkers, mortality, morbidity, quality of life, patient satisfaction, health care utilization, costs, or quality of care.

Findings Specific to Clinical Conditions

The volume of evidence varies sharply by clinical condition. We found the greatest volume of evidence for hypertension and depression, followed by hyperlipidemia, asthma, and diabetes. We did not find a substantial body of evidence testing varied approaches to inform several clinical conditions. Specifically, we found single-study bodies of evidence for myocardial infarction, glaucoma, and multiple sclerosis. For musculoskeletal diseases, we found two studies that used interventions with common features. We found no eligible studies for cancer; reasons likely include the restriction to patient-administered medications and outpatient settings. We found no eligible studies that explicitly focused on patients with adherence problems due to polypharmacy, although a few studies included patients with two or more conditions and assessed adherence to more than one medication.

Findings Specific to Interventions

Among the clinical conditions included in this review for which we identified multiple intervention approaches, we found the most consistent evidence that interventions improve medication adherence outcomes for hypertension, hyperlipidemia, congestive heart failure, and depression (Appendix G). We generally graded interventions as being beneficial with low to moderate strength of evidence, depending upon the specific type of intervention; these clinical conditions also included some interventions for which we found insufficient evidence. The evidence was less consistent for asthma and diabetes. For asthma, some interventions, such as self-management approaches or shared decisionmaking, were effective in improving medication adherence, but other approaches, such as offering health care providers access to patient

adherence data, suggested evidence of no benefit. For diabetes, the only trials that indicated evidence of benefit used care coordination and collaborative care approaches; all other approaches did not show evidence of benefit. We found the least consistent evidence of improvement in medication adherence for multiple chronic conditions: three trials, using pharmacist-based outreach, education, and problem-solving approaches, provided evidence of no benefit, and another trial, using case management, offered insufficient evidence.

Some intervention approaches tested across multiple clinical conditions include decision aids, case management, care coordination or collaborative care, telephone-based support, pharmacist-led multicomponent approaches, and mail-based education. One intervention, shared decisionmaking, has been tested in a single clinical area, asthma, with a single trial; without additional evidence, its widespread applicability is difficult to judge but it may well hold promise.

We note that these categories served as shorthand for one or more key elements of very diverse interventions. For instance, of the two trials categorized as interventions that gave health care providers access to patient adherence data, one included a substantial pharmaceutical care program, while the other did not. These examples illustrate that while the inductive approach we used to identify types of interventions allowed us to group interventions, it limited our ability to make conclusions about the effectiveness of specific intervention features. To address this limitation, KQ 3 offers further insights on common elements across these interventions.

Findings Specific to Outcomes

Table 99 through Table 102 present a summary of strength-of-evidence findings for medication adherence (Table 99), biomarkers and morbidity (Table 100), quality of life and patient satisfaction (Table 101), and lastly, healthcare utilization, costs, and quality of care (Table 102). We do not present a table for mortality: we found a single study providing insufficient evidence for patient access to medical records for congestive heart failure. Of the 29 types of interventions evaluated, 59 percent provided moderate or low evidence of benefit for medication adherence. The number of interventions that provided low or moderate strength of evidence progressively decreases for health, health care utilization outcomes, and other distal outcomes.

We found evidence of effective interventions to improve medication adherence for all chronic conditions, with the exception of multiple chronic conditions and multiple sclerosis (Table 99). The most promising interventions were self-management for asthma, and collaborative care or case management for depression (for short-term outcomes, rated moderate strength of evidence). For all other interventions, we found evidence of lower strength for medication adherence. Most often, we found insufficient evidence to judge benefit or lack of benefit; for some interventions we found low strength of evidence suggesting benefit for medication adherence; and for a few interventions, we found low strength of evidence of no benefit for medication adherence.

The most promising gains in health outcomes (that is, outcomes rated as moderate strength of evidence) were for depression case management for symptom improvement and pharmacist-led hypertension approaches for systolic blood pressure (Table 100). We rated evidence from all other interventions as low for benefit or insufficient. Our evaluation of evidence for patient satisfaction and quality of life did not reveal any evidence of moderate strength (Table 101). Evidence from one intervention for collaborative care for depression provided moderate strength of evidence of benefit for patient ratings of quality of care (Table 102). For all other

interventions, we either found low strength of evidence that the intervention provided benefit for health outcomes or we judged the evidence as being insufficient to evaluate benefit or lack of benefit.

Table 99. Summary of evidence for medication adherence

Strength of Evidence	Clinical Condition	Intervention
Benefit from intervention: moderate strength of evidence	Asthma[115-119]	Self-management
	Depression[129-132]	Collaborative care (telephone+in-person visits)
	Depression[84, 97, 125-127]	Case management
Benefit from intervention: low strength of evidence	Diabetes[83-85]	Care coordination and collaborative care
	Hyperlipidemia[91-93]	Telephone-based interventions (e.g., reminders, active problem management, tailored support)
	Hyperlipidemia[92, 94, 95]	Mail-based education (e.g., standard videos, tailored print)
	Hypertension[97-102]	Telephone-based education
	Hypertension[74, 103-107]	Pharmacist-led intervention (e.g., education, collaborative care, clinic)
	Hypertension[95, 108]	Mail-based education (e.g., standard videos, tailored print)
	Congestive heart failure[110]	Video and telephone reminders
	Congestive heart failure[111]	Pharmacist-led multicomponent
	Congestive heart failure[112]	Case management (multisetting)
	Myocardial infarction[114]	Mail-based communication to patients and providers about importance of medication adherence
	Asthma[122]	Shared decisionmaking
	Depression[134]	Reminder letters to nonadherent patients and monthly lists of nonadherent patients to providers
	Glaucoma[135]	Multicomponent including education, reminders, and dosing aid
	Multiple sclerosis[136]	Software-based telephone counseling
No benefit from intervention: low strength of evidence	Asthma[120, 121]	Pharmacist or physician access to patient adherence information
	Multiple or unspecified chronic conditions[139-141]	Pharmacist-based outreach, education, and problem solving
Insufficient evidence	Diabetes\hyperlipidemia[86-88]	Statin decision aids
	Diabetes[89]	Health coaching
	Diabetes[90]	Social support
	Hyperlipidemia[96]	Collaborative care
	Hyperlipidemia[74]	Pharmacist-led multicomponent (for 12 months)
	Hypertension[83, 90, 109]	Other interventions (e.g., collaborative care, nurse support, blister packing)
	Congestive heart failure[113]	Patient access to medical records and messaging system
	Myocardial infarction[114]	Mail-based communication to patients and providers about importance of medication adherence
	Depression[83, 128, 133]	Collaborative care (depression+HIV, depression+diabetes, telephone-only)
	Depression[123, 124]	Telemonitoring
	Musculoskeletal diseases[137, 138]	Case management
	Multiple or unspecified chronic conditions[142]	Case management

[a] Low for adherence

[b] Insufficient for persistence

Table 100. Summary of evidence for patient health outcomes: biomarkers and morbidity

Strength of Evidence Grade	Clinical Condition	Intervention	Specific Outcome(s)
Benefit from intervention: moderate strength of evidence	Hypertension	Pharmacist-led intervention (e.g., education, collaborative care, clinic)	Systolic blood pressure
	Depression	Case management	Depressive symptoms
Benefit from intervention: low strength of evidence	Diabetes	Care coordination and collaborative care	HBA1c Depressive symptoms
	Hypertension	Telephone-based education	Diastolic and systolic blood pressure
	Hypertension	Pharmacist-led intervention (e.g., education, collaborative care, clinic)	Diastolic blood pressure
	Asthma	Shared decisionmaking	Pulmonary function Asthma symptoms
	Depression	Case management	Diastolic and systolic blood pressure HbA1c
	Depression	Collaborative care	Major depression Moderately depressed
Insufficient	Diabetes	Social support	HbA1c
	Asthma	Self-management	Pulmonary function and inflammation markers Asthma symptoms
	Depression	Case management	Self-reported disability
	Depression	Collaborative care	Minor depression Severely depressed
	Glaucoma	Multicomponent including education, reminders, and dosing aid	Intraocular pressure

Note: Included evidence is limited to studies that found a benefit for medication adherence

Abbreviations: HbA1c: glycosylated hemoglobin; HIV: human immunodeficiency virus

Table 101. Summary of evidence for patient quality of life and patient satisfaction

Strength of Evidence Grade	Clinical Condition	Intervention	Specific Outcome(s)
Benefit from intervention: low strength of evidence	Diabetes\hyperlipidemia	Statin decision aids	Patient satisfaction
	Diabetes	Social support	Patient satisfaction
	Depression	Collaborative care	Patient satisfaction
	Congestive heart failure	Pharmacist-led multicomponent	Patient satisfaction
	Asthma	Shared decisionmaking	Quality of life
No benefit from intervention: low strength of evidence	Asthma	Self-management	Quality of life
Insufficient	Depression	Collaborative care	Quality of life
	Hyperlipidemia	Pharmacist-led multicomponent (for 12 months)	Patient satisfaction
	Hypertension	Pharmacist-led intervention (e.g., education, collaborative care, clinic)	Quality of life Patient satisfaction
	Hypertension	Other interventions (e.g., collaborative care, nurse support, blister packing)	Patient satisfaction
	Congestive heart failure	Video and telephone reminders	Quality of life
	Congestive heart failure	Pharmacist-led multicomponent	Quality of life
	Congestive heart failure	Patient access to medical records and messaging system	Quality of life Patient satisfaction
	Musculoskeletal diseases	Case management	Patient satisfaction

Note: Included evidence is limited to studies that found a benefit for medication adherence

Table 102. Summary of evidence for healthcare utilization, costs, and quality of care

Strength of Evidence Grade	Clinical Condition	Intervention	Specific Outcome(s)
Benefit from intervention: moderate strength of evidence	Depression	Collaborative care	Quality of care
Benefit from intervention: low strength of evidence	Hypertension	Pharmacist-led intervention (e.g., education, collaborative care, clinic)	Hospital visits and other contacts
	Congestive heart failure	Pharmacist-led multicomponent	All-cause ED visits and all-cause ED visits + hospitalizations
	Asthma	Shared decisionmaking	Healthcare utilization
Insufficient	Hypertension	Pharmacist-led intervention (e.g., education, collaborative care, clinic)	Other measures of healthcare utilization
	Congestive heart failure	Pharmacist-led multicomponent	All-cause ED visits and all-cause ED visits + hospitalizations Other measures of healthcare utilization Costs
	Congestive heart failure	Case management (multisetting)	Healthcare utilization
	Congestive heart failure	Patient access to medical records and messaging system	Healthcare utilization
	Depression	Collaborative care	Healthcare utilization Costs

Note: Included evidence is limited to studies that found a benefit for medication adherence

Abbreviations: ED: emergency department

Key Question 2. Effect of Policy Interventions on Medication Adherence and Other Outcomes

Only three studies evaluated the effects of policy-level interventions on medication adherence. These studies addressed adherence to medications used to treat cardiovascular disease, diabetes, and respiratory conditions. All three studies used retrospective cohort designs and assessed medication adherence using insurance claims data to measure either the medication possession ratio (MPR) or proportion of days covered (PDC). The use of similar adherence measures across the studies facilitates comparing their results. All three studies evaluated policy-level interventions that reduced patient out-of-pocket expenses for prescription medications, either through reduced medication copayments or improved prescription drug coverage. The study by Zhang and colleagues evaluated the impact of Medicare Part D on medication adherence among groups of older adults who had different levels of prescription drug coverage prior to implementation of Medicare Part D.[148] This study found a large improvement in adherence among individuals who had no prescription drug coverage prior to Medicare Part D and smaller improvements among individuals with some prior coverage, but whose out-of-pocket expenses were reduced following Medicare Part D implementation.

Both studies evaluating the impact of reduced copayment on medication adherence also found statistically significant between-group differences in adherence to medications used to treat cardiovascular conditions and diabetes, favoring the group who had their copayment reduced. However, we find these differences somewhat difficult to interpret because medication adherence decreased over time in all groups in both of these studies. Still, the magnitude of effects observed in these two studies were similar to those observed by Zhang and colleagues among individuals who had some prescription drug coverage prior to Medicare Part D, but who experienced a reduction in out-of-pocket medication expenses following its implementation.[148] Therefore, we concluded that there is moderate strength of evidence indicating that policy-level interventions that reduce patient out-of-pocket expenses can have a beneficial effect on adherence to medications used to treat cardiovascular conditions and diabetes (Table 103).

Only one study evaluated the effects of policy-level interventions on adherence to medications used to treat respiratory conditions. This study found no effect on medication adherence. Therefore, we concluded that there is insufficient evidence to draw conclusions for the effectiveness of these types of interventions in this clinical area (Table 103).

None of the studies examined the effect of policy-level interventions on more distal outcomes (e.g., morbidity, mortality, health service utilization). We consider this a major gap in the literature.

Table 103. Summary of evidence for policy-level interventions

Clinical Condition	Intervention	Comparator	Number of Studies	Medication Adherence	Other Outcomes
Cardiovascular disease[146-148]	Improved prescription drug coverage	Unchanged prescription drug coverage	3	Benefit: moderate SOE	No evidence
Diabetes[146, 148]	Improved prescription drug coverage	Unchanged prescription drug coverage	2	Benefit: moderate SOE	No evidence
Respiratory conditions[146]	Reduced medication copy	Unchanged medication copay	1	Insufficient SOE	No evidence

Abbreviations: SOE, strength of evidence.

Key Question 3a. Characteristics of Medication Adherence

Overall, the extreme heterogeneity of terminology used to describe medication adherence interventions in the studies reviewed hindered the ability to compare effects of different features of the interventions across studies and across diseases. Moreover, heterogeneity of the interventions themselves made identification of "intervention type" clusters challenging. Most, but not all, studies provided information, though not in a standardized manner, about six key intervention characteristics, which included the target(s), the agent(s), and the mode(s) of the intervention, as well as their intensity, duration, and components. The characteristics provided a framework by which we could describe the interventions. For example, for the intervention target, a little over half of the interventions were aimed at a combination of multiple targets, whereas nearly 40 percent targeted only patients. Similarly, for the agent of intervention delivery, a pharmacist, physician, or nurse delivered about half of interventions. About half of interventions involved at least some face-to-face delivery of the program.

In addition to characterizing the interventions for each of these six key features, we also identified some general patterns of combinations of the six features. For example, while interventions varied in the number of contacts they entailed from 1-30, those with more contacts tended to involve phone contact. Similarly, certain intervention components, such as facilitation and knowledge-based components affecting the delivery of medical information, were commonly used across most interventions, whereas others, such as motivational interviewing and contingent rewards were used less commonly. Similarly, we noted a greater frequency of combining awareness-raising activities with knowledge delivery among nurse-delivered compared with pharmacist- and physician-delivered interventions. The components of the intervention were the least well-characterized aspect, although often the feature that most meaningfully distinguished them. Some intervention types, such as decision aids, were not captured by existing taxonomies of adherence intervention components.

Key Question 3b. Direct Comparisons of Medication Adherence Intervention Components

The vast majority of studies compared a multicomponent intervention to a "usual care" control arm. Few studies directly compared one feature of an intervention to another feature to determine which aspects of the intervention had the most effect on outcomes. Among the three studies that conducted this kind of comparison, each compared different aspects of different interventions. As a result, we could not pool across the three studies. Within those three studies, one demonstrated that shared decisionmaking had a greater effect on adherence to asthma medications than did a clinical decision-making approach, while both were more efficacious than usual care. Moreover, the effects of shared decisionmaking on adherence lasted up to 2 years whereas those due to clinical decisionmaking had attenuated at that point. Another study, conducted among patients with congestive heart failure, directly compared two different delivery modes (telephone versus videophone). This study found no difference between the two delivery modes regarding improvement in adherence: both were superior to usual care. Another study directly compared the agent of delivery (physician versus research staff) using the same mode (face-to-face) to deliver a decision aid among patients with diabetes deciding whether to take statins to lower their risk of cardiovascular disease. The effects were the same regardless of who delivered them: the decision aid had greater improvement on adherence than usual care, regardless of who delivered the aid.

It appears that mode of delivery was an important feature only in certain settings. Moreover, agent of delivery does not appear to be important in the setting studied for the decision aid studied. However, shared decisionmaking seems more effective than clinical decisionmaking at improving and sustaining improvement in adherence to asthma medication. Shared decisionmaking also appeared to improve pulmonary function tests when compared with clinical decisionmaking but did not improve quality of life or health care utilization; we rated this evidence as having low strength (Table 104).

Key Question 4. Outcomes for Vulnerable Populations

We searched for evidence on a broad set of vulnerable populations and found varying degrees of strength of evidence. For certain vulnerable subgroups (specifically for patients with major depression, severe depression, multiple chronic conditions or depression with hypertension comorbidity, African-American patients with depression and diabetes comorbidity, elderly patients with diabetes, hyperlipidemia, congestive heart failure, or hypertension), we determined that there was low strength of evidence of interventions having a positive impact on medication adherence. We found low strength of evidence of no benefit of interventions on adherence for interventions dealing with patients who had depression with HIV comorbidity, and diabetes with depression comorbidity. The low number of studies and limited sample size of included studies curtailed our confidence in the strength of evidence. For some vulnerable subgroups, including low-income, populations with low health literacy, we did not find any evidence.

Key Question 5. Adverse Effects

Our review of studies that examined adverse events or harms associated with interventions aimed at improving adherence did not find any indication that these interventions result in any unintended consequences for patients. However, we found only three relevant studies, and the level of heterogeneity between these studies in terms of the intervention and outcomes was so significant that we determined insufficient evidence existed to reach definitive conclusions.

Table 104. Direct comparisons of medication adherence intervention components: strength of evidence summary table

Clinical condition	Intervention	Comparator	Number	Medication Adherence	Mortality	Biomarkers	Morbidity	Quality of Life	Health Care Utilization
Asthma}#1988 Wilson, 2010}	Shared decisionmaking	Clinician decisionmaking	1	Benefit: low SOE	No evidence	Benefit: low SOE	Insufficient	No benefit: Low SOE	No benefit: Low SOE
Congestive heart failure[110]	Telephone reminders	Video reminders	1	Insufficient	No evidence	No evidence	No evidence	No evidence	No evidence
Diabetes[86]	Decision aids delivered by clinician	Decision aids delivered by research staff	1	Insufficient	No evidence	No evidence	No evidence	No evidence	No evidence

Abbreviation: SOE, strength of evidence.

Findings in Relationship to What is Already Known

This review contributes to the sizeable literature of medication adherence in several ways. A Cochrane review in 2008[7] demonstrated that medication adherence interventions can have moderate effects on medication adherence and health outcomes for several common chronic and acute medical conditions, including studies through 2007. Our review, as it is more recent, includes studies after 2007. In contrast to the Cochrane review, because adherence to infectious diseases differs in several ways from those of chronic illnesses and since several recent reviews of HIV medication adherence interventions had been conducted,[76, 151] we excluded studies of HIV and other infectious and acute conditions, whereas the Cochrane review included these. Hence, we are unable to comment on adherence interventions in these studies. We also, like the Cochrane review, excluded substance abuse interventions, but we also excluded studies of adherence to medications for severe psychosis because these conditions require specific approaches that would not apply in other diseases. The Cochrane review only included adherence studies that also assessed health outcomes. To broaden our understanding of the impact of interventions on adherence, we included adherence intervention trials even if they did not assess other health outcomes. This inclusion likely expanded the variety of medication interventions included in the review. This review was also more expansive in including interventions that assessed the effects of policy-level interventions: we found moderate strength of evidence that interventions that reduce the amount of out-of-pocket expenses incurred by patients improves medication adherence.

Unlike other reviews, this review identified intervention effects in relation to intervention type, to identify those interventions for which the strongest evidence exists. This information has the potential to offer actionable information for policymakers and practitioners working within clinical domains. This review has also characterized interventions based on a standardized, comprehensive set of features. This information regarding medication adherence intervention features has not been reported previously and provides a framework by which interventionists and researchers may develop, test, and report their adherence programs in a more explicit and standardized manner. Ultimately, if studies were to use this framework more consistently, pooling of data from future studies would allow more powerful analyses to be conducted across studies.

Finally, this is the first review of medication adherence randomized controlled trials (RCTs) to attempt to understand the moderating effects of population characteristics on intervention effects by characterizing the evidence available for intervention efficacy among vulnerable populations. The findings of this review regarding the paucity of evidence in this area highlights the need for future studies include vulnerable populations.

Applicability

The interventions included in this review were not highly selective nor did they limit themselves to narrow or unrepresentative disease severity. An additional factor contributing to overall applicability includes the large variety of clinical conditions.. The interventions themselves spanned the range from minimalist to intense and minimalist, although evidence often came from small studies. Because this diversity in types of clinical condition and interventions is not supported by replication of studies in different settings, the findings are limited in their applicability. Another limitation to the applicability of the evidence comes from the complexity of multicomponent interventions. Studies did not generally provide information on the extent to

which active ingredients in interventions were identified, operationalized, and translated into instructions and manuals for replication. The degree to which these interventions require fidelity to protocol when implemented in nontrial settings is also unclear, further limiting the applicability of the evidence.

Implications for Clinical and Policy Decisionmaking

We found evidence of effective interventions to improve medication adherence for most chronic conditions, suggesting that medication adherence to chronic medication can be improved through intervening with patients, providers, health systems, or policy and that a broad range of approaches can work. Adherence is the result of a combination of patient, provider, and policy factors, and hence most interventions we identified were multifactorial; over half aimed at multiple targets and most had multiple components, including several with multiple delivery modes. In other words, there is no one magic bullet for medication adherence. We found the strongest evidence for enhancing adherence with self-management of asthma (for short-term outcomes) and collaborative care or case management for depression. We found the strongest evidence with depression case management for depression symptom improvement and pharmacist-led hypertension approaches for systolic blood pressure improvement.. These findings suggest that clinicians should consider adherence interventions for their chronically ill patients, particularly self-management for asthma, case management for depression, and involvement of a pharmacist trained in adherence management for care of hypertension.

Clinicians and policymakers should keep in mind that we found very little evidence of the relationship of improved medication adherence and adverse events, although what we found suggests that improving adherence does not increase the incidence of adverse events. This was the first review we are aware of that systematically reviewed information on adverse events and so provides promising information that should be confirmed in future studies and reviews.

The lack of studies evaluating potential mechanisms that link improved adherence to other outcomes limits policymakers' and clinicians' ability to use an "a la carte" approach to implementing components of complex interventions to enhance patients' medication adherence. Therefore, future studies need to do a better job not only of clearly describing each component of their intervention but also of designing studies and conducting analyses that can identify which components are driving the effects of the intervention.

Poor medication adherence is known to result in large upstream health care costs. An important finding for policymakers contemplating changes in health policy is our assessment of moderate evidence, from three consistent studies, that reducing patients' out-of-pocket costs can improve their medication-taking behavior. Policies that enhance patient adherence by easing patient copayments or other patient paid medication expenses may prove highly cost-effective. Cost-effectiveness studies that assess the long term effects of such policies could be beneficial to policymakers.

Limitations of the Comparative Effectiveness Review Process

The constraints for population and setting we imposed on the systematic review serve as limitations to the applicability of the review. As noted earlier, we did not review the evidence on populations with human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), mania, bipolar disorder, or substance abuse. Interventions for these excluded

clinical conditions may have applicability to the conditions that we included in our review. Another limitation is that of setting: we excluded non-English and non-U.S. studies. This criterion likely substantially decreased the pool of eligible studies but their applicability to the United States is unclear. Finally, our inductive approach to categorizing interventions for KQ 1, in the absence of an overarching taxonomy, resulted in intervention labels that did not fully describe or account for heterogeneity within and across clinical areas. This approach limits our ability to make statements about the effectiveness of interventions across clinical areas.

Limitations of the Evidence Base and Research Gaps

Methodological Limitations

Our review identified several gaps in the literature that may be filled by future research efforts. In many disease areas for KQ 1, interventions and adherence measures were heterogeneous, which limited the ability to pool results from studies. The use of more standardized, objective adherence outcomes in future research could help results from studies become more interpretable in the context of other adherence studies. In addition, a lack of focus on mediating relationships through which the interventions acted on medication adherence limited the conclusions that could be drawn about the efficacy of specific intervention features. Moreover, while some studies showed that interventions improved adherence, only a few had large effects on adherence. Hence, future studies could be designed to identify how to enhance the effects of efficacious interventions, such as by using a factorial design that combines efficacious interventions and can assess both additive and multiplicative effects. At a minimum, the use of SQUIRE guidelines will improve the quality of reporting so that future studies of complex interventions routinely clarify the mechanisms by which intervention components are expected to cause change, the course of the implementation, and the success of tests of the mechanism of action.[152] Although many studies did assess some health outcomes, the inclusion of long-term health outcomes in all studies of adherence would enhance capacity to assess overall significance of adherence interventions. This would also facilitate cost-effectiveness analyses of such interventions.

Key Question 1. Patient, Provider, and Systems Interventions

Key Question 1. Diabetes

The body of evidence for diabetes was relatively sparse and provided evidence of low strength. The evidence did not clarify which aspects of the various models were important. Future studies would benefit from factorial designs that identify which aspects of interventions are most important, which are working together, and which are having an independent influence. Additional research to assess such models in a wide range of settings, on a larger scale, and over a longer term would be particularly valuable. Also, studies that seek to advance understanding whether the impact of interventions for diabetes medications vary for different subgroups (such as groups with low health literacy, very poorly controlled diabetes, or other vulnerable populations) may be beneficial. This can be accomplished by assessing the moderating effects of such characteristics as literacy level on the effects of the intervention on adherence. Most but not all studies included HbA1C assessments. It is important that future studies include such important biomarkers as outcome measures. One trial that found an effect of a decision aid on medication adherence also assessed the effects of the intervention on patient satisfaction. No

trials assess costs or health care utilization. Inclusion of assessments of intervention effects on patient satisfaction and other outcomes, costs, quality of care, utilization, or quality of life in future studies will be important.

Key Question 1. Cardiovascular Disease (Heart Failure, Hypertension, and Myocardial Infarction) and Hyperlipidemia

We found that interventions and measures of adherence were heterogeneous among included trials evaluating interventions to improve adherence in patients with cardiovascular disease and hyperlipidemia. This heterogeneity limited our ability to pool results within respective disease categories. Among studies in cardiovascular disease and hyperlipidemia, reporting of additional outcomes beyond medication adherence varied by disease. For example, all four heart failure trials found improved medication adherence and reported additional outcomes, including health care utilization in three of them. Among the 15 trials conducted in patients with hypertension, seven found improved adherence or persistence, six of which reported systolic and diastolic blood pressure outcomes, but only two of which reported health care utilization outcomes. Among the nine trials in hyperlipidemia, five found either improvements in medication adherence, persistence or initiation; only two of the five reported additional outcomes, including low-density lipoprotein cholesterol (LDL-C) levels and patient satisfaction. Thus, while a majority of trials in the heart failure section evaluated health care utilization outcomes, few trials with improved adherence in the hypertension group and none with improved adherence in the hyperlipidemia group reported such outcomes. Future research could help to fill this gap.

The identification of only one trial of medication adherence in patients with myocardial infarction suggests significant research gaps in this area. Not only are studies needed that simply evaluate adherence interventions in patients after myocardial infarction, but also evaluation of how such interventions affect clinical outcomes will be important.

We noted that quality of life and patient satisfaction were evaluated in few trials and that cost was evaluated in only one trial, conducted in patients with heart failure. Quality of care was not evaluated in any of the included cardiovascular disease trials. Future research could also enhance our understanding of how medication adherence interventions could affect these outcomes as well.

Key Question 1. Asthma

Among included asthma trials, we found that no long-term outcomes were reported for short-term interventions; this issue was true for many of the trials included in this reviewfor other clinical conditions as well. For asthma, interventions lasting 4-6 weeks generally only reported outcomes within the intervention period or a month thereafter. Six of eight interventions for asthma-related medication adherence reported improvement in medication adherence; unlike other clinical conditions, all of these studies also reported health outcomes. Our review of the evidence for asthma did not find any information on patient satisfaction, costs, or quality of care. We found a single trial on a potentially promising approach, shared decisionmaking. Further research on this intervention will help to clarify its applicability to other settings.

Key Question 1. Depression

Eight out of 12 depression interventions reported improvements in medication adherence, with seven of these trials reporting on health outcomes. However, these trials provide limited information on patient satisfaction, costs, and quality of care. We found one trial that met our

criteria on the use of reminder letters to nonadherent patients and lists of nonadherent patients to their health care providers. An added limitation of the evidence base was the lack of information on the clinical utility of medication adherence improvements. For example, one trial found a 1–3 percent statistically significant difference between the intervention and control arms of the study. A better understanding of the clinical implications of this difference in medication adherence requires that future research evaluate the effects of the intervention on clinical outcomes in addition to medication adherence outcomes.

Key Question 1. Other Chronic Conditions.

For interventions in the areas of unspecified or multiple chronic conditions, glaucoma, multiple sclerosis (MS), and musculoskeletal diseases, we found only a few trials overall that met our inclusion criteria. In many cases we only identified one trial per disease area that met our inclusion criteria, indicating significant research gaps in these disease areas. For example, among included studies dealing with unspecified or multiple chronic conditions, we found four trials that varied in the intervention used and outcomes reported. One of the trials showed no effect of the intervention on adherence and mentioned that a post-hoc study showed the intervention may actually be inferior to usual care in improving medication adherence. For the other three trials, the variation among studies was too significant to meaningfully assess the evidence. More studies focused on multiple chronic conditions are required to fill this gap. For glaucoma and MS, where we found only one trial each, more studies with larger sample size and lower risk of bias are required to reach meaningful conclusions regarding interventions to improve adherence to medication. We found two trials dealing with musculoskeletal diseases, but again, were unable to reach conclusions due to a lack of precision in the results and significant differences in the nature of the interventions and the outcomes measured.

Key Question 2. Policy-Level Interventions

The findings from the three studies investigating policy-level interventions suggest that reduced copayments and improved insurance coverage for prescription medications may improve medication adherence. However, none of the studies examined the effect of these policy changes on any other health outcomes. Thus, we found no evidence that these types of interventions improve disease control, as might be indicated by improvements in blood pressure, lipid levels, or other biologic measures; long-term health outcomes (e.g., myocardial infarctions, strokes); or health care utilization. This gap in the knowledge base needs to be addressed in future research. In addition, none of the studies examined whether the impact of these interventions varied across different population subgroups. For example, it seems likely that policy-level interventions designed to reduce out-of-pocket costs would have the greatest effect among individuals with limited incomes and those using several medications. However, this question remains to be answered by future research. Finally, because the studies investigating the effect of copayment reductions found that adherence decreased in all study groups over time, research using new user designs is needed to better understand how policy-level interventions may change the trajectory of adherence over time, beginning at the initiation of therapy.

Key Question 3. Intervention Characteristics

In KQ 3, we sought to characterize and describe the features of medication adherence interventions in a meaningful manner. In reviewing studies, we found at least six aspects of such interventions by which they varied: their target, agent, mode, intensity, duration, and

components. Our capacity, however, to describe the variation in these features was limited by heterogeneity not only of adherence measures used, but also of the language used to describe the intervention features. We suggest that future studies of medication adherence interventions adopt a standardized manner for describing such interventions that includes a clear report of the intended targets of the intervention, all agents, and modes of delivery using the categories we have identified here. Moreover, we believe that it would be quite simple for studies to describe the intensity and duration of all interventions in a similarly standardized manner that included the total number and type of contacts, the total amount of time for each contact, the frequency of the contacts, and the duration of calendar time over which the contacts are delivered. For interventions that do not involve contacts per se, such as policy changes, these variables would be categorized as "not applicable." Much as specifications of CONSORT statement enhanced capacity to compare and pool clinical trial results across studies,[153] such a simple step as standardizing this reporting descriptions of interventions would go a long way to enhancing capacity to understand the effects of different aspects of these intervention. Similarly, we would recommend that deBruin's taxonomy[70] be used to report intervention components by researchers of medication adherence interventions so that the inclusion of these components could also be catalogued comprehensively for comparison of their utility across studies. Finally, we found only three studies that directly compared specific components or approaches of interventions. While more standardized descriptions of interventions will enhance capacity to pool data across studies and efficiently compare effects of specific features, as we gain insight into what features are most critical, more studies will be needed that directly compare aspects of interventions. Moreover, given that some coordinated care and other multicomponent interventions appear to be effective, study designs, such as factorial or step-wedged approaches that may help to delineate both the additive and synergistic aspects of multicomponent interventions will be particularly beneficial.

Key Question 4. Vulnerable Populations

Our examination of the literature regarding medication adherence among vulnerable populations showed several research gaps. We found no studies for the following vulnerable subpopulations we intended to examine as part of our inclusion criteria: racial and ethnic minorities with the exception of those who identified as African-American; populations with certain specific special health needs such as low literacy, low-income populations. Among vulnerable populations for which we did find a few studies, the strength of evidence was low, indicating that more focus is required in this area. For example, we found only a single study that examined medication adherence in patients with depression and diabetes.

Key Question 5. Adverse Events

In our examination of adverse events, harms, and unintended consequences, we did not find any indication that interventions designed to improve medication adherence result in an increase in such events. However, we found only three studies for this portion of the review, indicating that examination of adverse events related to attempts to improve adherence has not received sufficient attention in the literature. The significant variation in the study design and outcomes for these studies limited our ability to evaluate the strength of the evidence.

Finally, while not the goal of this review, there appeared to be a paucity of post-trial qualitative studies to understand from the patients' perspective the aspects of the interventions

that they found most useful. Use of such mixed methods may inform the refinement of efficacious interventions to make them most effective in real-world settings.

Conclusions

Despite heterogeneity of adherence measurement, interventions tested, and characterization of interventions, we found a few nonpolicy-level interventions for which there was moderate evidence of benefit to improve medication adherence and health outcomes: self-management for short-term improvement in adherence to asthma medications, collaborative care or case management for short-term improvement of adherence to depression medications, and symptoms and pharmacist-led hypertension approaches for systolic blood pressure improvement. There was also moderate strength of evidence that policy-level interventions that reduce the amount of out-of-pocket expenses incurred by patients improves medication adherence. We found low strength of evidence for many other interventions; these diverse groups of approaches offer promise but require more research to establish greater strength of evidence. Less evidence existed, however, for interventions that benefited health outcomes along with medication adherence. Several reviews that researchers have conducted over the last two decades along with this one confirm that medication adherence can be improved via intervention. At this stage, new studies need to be asking “What specific intervention element or elements work best for improving medication adherence?” and “How can we further enhance medication adherence interventions to improve health outcomes?”

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