Evidence Report/Technology Assessment
Number 208

4. Medication Adherence Interventions: Comparative Effectiveness

Closing the Quality Gap: Revisiting the State of the Science

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Evidence-Based Practice

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Closing the Quality Gap: Revisiting the State of the Science

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The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

In 2004, AHRQ launched a collection of evidence reports, Closing the Quality Gap: A Critical Analysis of Quality Improvement Strategies, to bring data to bear on quality improvement opportunities. These reports summarized the evidence on quality improvement strategies related to chronic conditions, practice areas, and cross-cutting priorities.

This evidence report is part of a new series, Closing the Quality Gap: Revisiting the State of the Science. This series broadens the scope of settings, interventions, and clinical conditions, while continuing the focus on improving the quality of health care through critical assessment of relevant evidence. Targeting multiple audiences and uses, this series assembles evidence about strategies aimed at closing the "quality gap," the difference between what is expected to work well for patients based on known evidence and what actually happens in day-to-day clinical practice across populations of patients. All readers of these reports may expect a deeper understanding of the nature and extent of selected high-priority quality gaps, as well as the systemic changes and scientific advances necessary to close them.

AHRQ expects that the EPC evidence reports will inform consumers, health plans, other purchasers, providers, and policymakers, as well as the health care system as a whole, by providing important information to help improve health care quality.

We welcome comments on this evidence report or the series as a whole. Comments may be sent by mail to Carmen Y. Kelly, Pharm.D., M.P.H., R.Ph., Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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

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Medication Adherence Interventions: Comparative Effectiveness

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Structured Abstract

Objectives. To assess the effectiveness of patient, provider, and systems interventions (Key Question [KQ] 1) or policy interventions (KQ 2) in improving medication adherence for an array of chronic health conditions. For interventions that are effective in improving adherence, we then assessed their effectiveness in improving health, health care utilization, and adverse events.

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 and the effectiveness of interventions for a range of vulnerable populations. Two reviewers graded the strength of evidence using established criteria.

Results. We found a total of 62 eligible studies (58 trials and 4 observational studies) from our review of 3,979 abstracts. These studies included patients with diabetes, hyperlipidemia, hypertension, heart failure, myocardial infarction, asthma, depression, glaucoma, multiple sclerosis, musculoskeletal diseases, and multiple chronic conditions. Fifty-seven trials of patient, provider, or systems interventions (KQ 1) evaluated 20 different types of interventions; 4 observational studies and one trial of policy interventions (KQ 2) evaluated the effect of reduced out-of-pocket expenses or improved prescription drug coverage. We found the most consistent evidence of improvement in medication adherence for interventions to reduce out-of-pocket expenses or improve prescription drug coverage, case management, and educational interventions across clinical conditions. Within clinical conditions, we found the strongest support for self-management of medications for short-term improvement in adherence for asthma patients; collaborative care or case management programs for short-term improvement of adherence and to improve symptoms for patients taking depression medications; and pharmacist-led approaches for hypertensive patients to improve systolic blood pressure.

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 regarding long-term medication adherence or health outcomes.

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Executive Summary

Background

Achieving the goal 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 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 treatment, however, provides an additional explanation for the incongruity between recommended treatment and actual treatment outcomes.

Poor medication adherence is relatively 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] Nonadherence has been estimated to cost the U.S. health care system between $100 billion and $289 billion annually in direct costs.[3,5,17-20] 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.[21-27]

Scope and Key Questions

This review seeks to synthesize evidence regarding the efficacy and effectiveness of interventions to improve medication adherence among adults across a broad array of chronic conditions. This report is part of a larger initiative, the Closing the Quality Gap: Revisiting the State of the Science series. This series builds on the Agency for Healthcare Research and Quality (AHRQ) 2004–07 collection of publications, Closing the Quality Gap: A Critical Analysis of Quality Improvement Strategies, which summarized the evidence on quality improvement strategies for chronic conditions.[28] 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 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:

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 A.

Methods

Topic Refinement

Topics for the Closing the Quality Gap: Revisiting the State of the Science series were solicited from the leads of AHRQ portfolios (areas of research). 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, timing, 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.

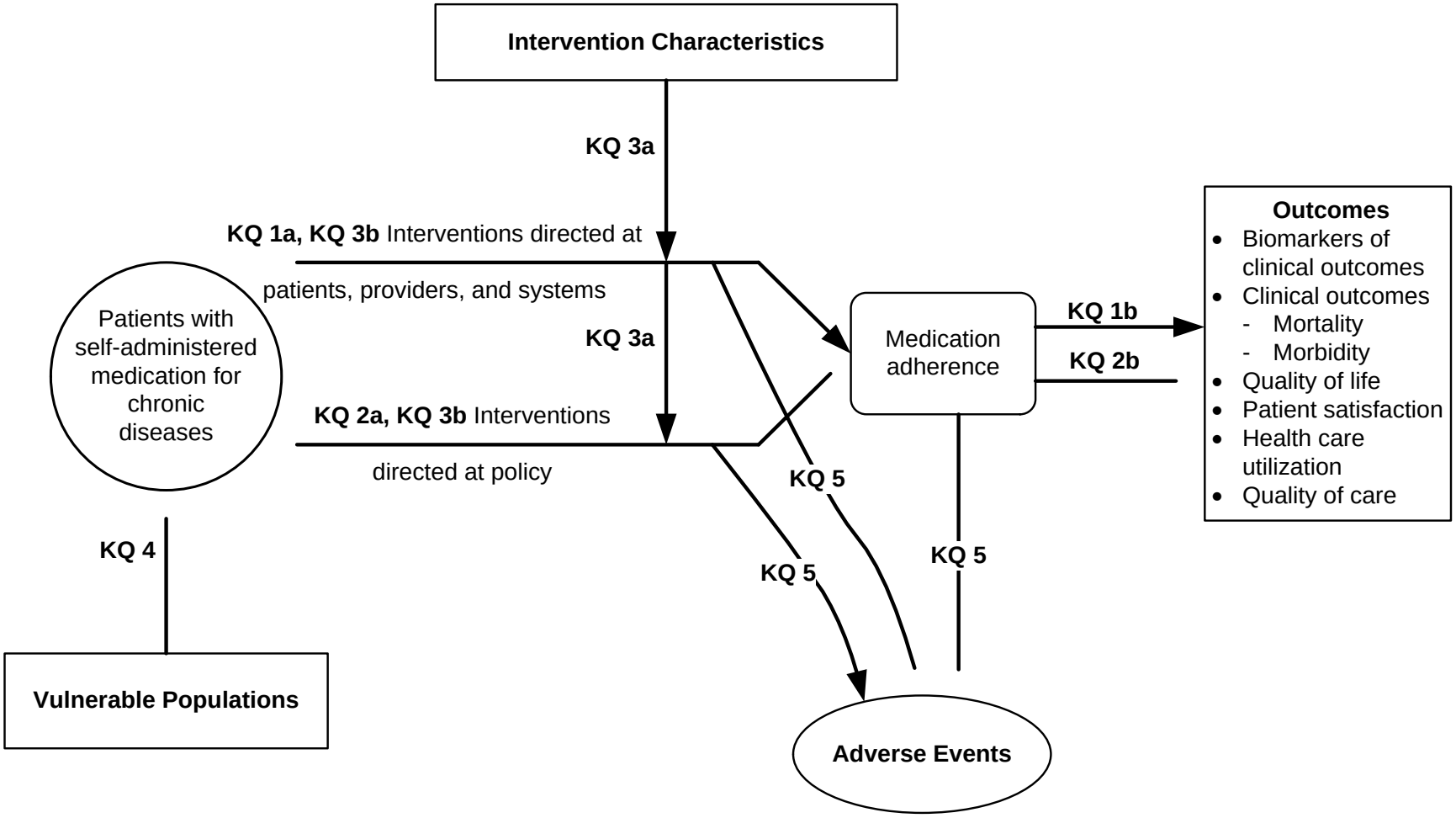
Literature Search and Review Strategy

To identify articles relevant to each KQ, we conducted targeted searches using MEDLINE®, Cochrane Library, and the Cochrane Central Trials Registry. (Appendix A of the main report lists search terms.) We reviewed our search strategy with TEP members 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 performed a full-text review for eligibility against our inclusion/exclusion criteria (Table A). During full-text review, if both reviewers agreed that a study did not meet 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.

Figure A. Analytic framework



Abbreviations: KQ = Key Question.

Table A. Inclusion and exclusion criteria

Category	Inclusion Criteria	Exclusion Criteria
Population	• Adults prescribed self-administered medication for secondary or tertiary prevention of chronic diseases	• Children under age 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	• Outside United States
Time period	• 1994 to present	• Pre-1994
Length of followup	• No limit	
Settings	• Outpatient primary and specialty care settings • Community-based settings • Home-based settings	• 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	• All other outcomes when interventions did not yield a statistically significant improvement in medication adherence
Publication language	• English	• All other languages
Admissible evidence for Key Question 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 as having high risk of bias • Studies with historical rather than concurrent control groups • N <40

Table A. Inclusion and exclusion criteria (continued)

Category	Inclusion Criteria	Exclusion Criteria
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 as having high risk of bias • N <40

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[29] and specified in the RTI Item Bank.[30] We resolved disagreements between the two reviewers by consulting an experienced member of the team.

Data Synthesis

For KQ 1, results are categorized by clinical condition. For KQs 2 and 3, results are categorized by intervention characteristics. We specified all nonmorbidity data a priori and 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. For 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. If three or more studies were similar (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 (due, for example, to heterogeneity, insufficient numbers of similar studies, or insufficiency or variation in outcome reporting), we synthesized the data qualitatively. For KQ 4, 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 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) based on the guidance established for the EPC program.[31] This approach incorporates four key domains: risk of bias (including study design and aggregate quality), consistency, directness, and precision of the evidence.

Definitions of the grades of overall strength of evidence[31] are as follows:

- 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.

Applicability

We assessed the applicability of the evidence following guidance from Atkins and colleagues.[32] We used the PICOTS framework to explore factors that affect or limit applicability.

Results

We provide a summary of results by KQ. For KQs 1 and 2, we synthesized the evidence by clinical condition and type of intervention. For KQs 3, 4, and 5, we synthesized the evidence for all studies relevant to KQs 1 and 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 strength-of-evidence grades.

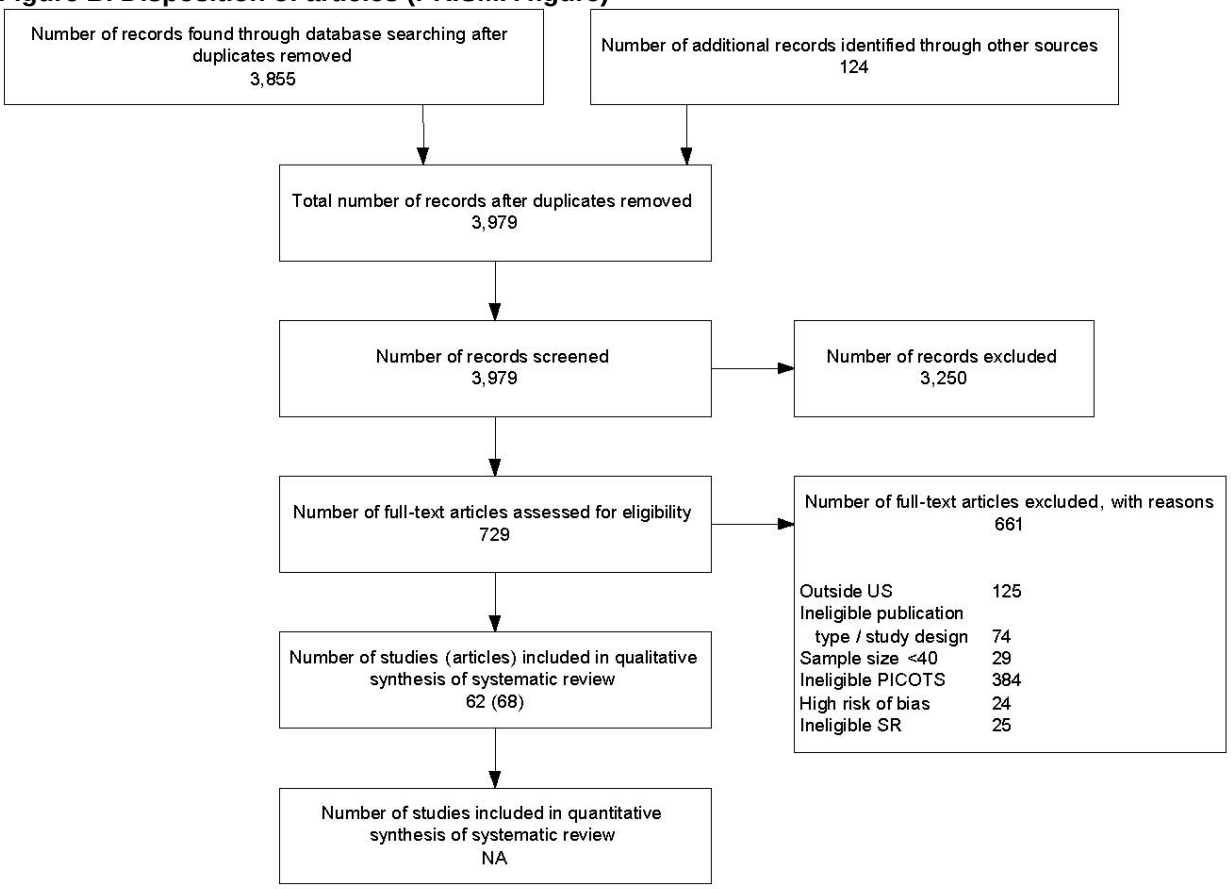
Results of Literature Searches

Figure B presents our literature search results. Literature searches through December 8, 2011, for the current report identified 3,855 unduplicated citations. Hand searches of systematic reviews and other sources added a total of 124 citations. All these sources produced a total of 3,979 references.

After applying our eligibility and exclusion criteria to titles and abstracts of all identified citations, we obtained full-text copies of 729 published articles. We reapplied our inclusion criteria and excluded 661 articles.

The 68 articles included in this review for all KQs represent 62 studies. 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 strength-of-evidence tables. Of the 68 included articles, 64 were randomized controlled trials (RCTs) and 4 were observational studies. Among the trials, 51 used a parallel randomization scheme, 12 used cluster randomization, and 1 used stratified randomization. Among the observational studies, 2 used a before-after design, 1 used an interrupted time series design with a concurrent control group, and 1 used a retrospective quasi-experimental design. We assessed 57 included articles as having medium risk of bias and 11 as having low risk of bias.

Figure B. Disposition of articles (PRISMA figure)



Abbreviations: NA = not applicable; PICOTS = populations, interventions, comparators, outcomes, timing, and settings; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SR = systematic review.

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 57 trials in 63 articles included in this comparative effectiveness review suggests that numerous pathways provide opportunities to improve medication adherence across clinical conditions. These approaches 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; such interventions often require some, or even a good deal of, restructuring of typical approaches to health care delivery in the United States.

Despite such evidence about promising approaches to improving medication adherence, only a subset of these effective interventions relates better adherence with better health outcomes or other important end results. We found relatively little evidence linking improved adherence to

improvements in other outcomes, such as biomarkers, morbidity, mortality, quality of life, quality of care, patient satisfaction, health care utilization, and costs.

Findings Specific to Clinical Conditions

The volume of evidence regarding improving medication adherence differs sharply by clinical condition. We found the greatest amount of evidence, in terms of numbers of trials or studies, numbers of subjects, or both, for hypertension and depression, followed by hyperlipidemia, asthma, and diabetes. The clinical conditions for which results are summarized in Table B are diabetes,[33-37] hyperlipidemia,[35,38-46] hypertension,[35,36,43,46-61] heart failure,[62-65] myocardial infarction,[66] asthma/chronic obstructive pulmonary disease,[67-74] depression,[33,48,75-86] glaucoma,[87] multiple sclerosis,[88] musculoskeletal diseases,[89-91] and multiple or unspecified conditions.[92-95] We did not find a substantial body of evidence testing varied approaches for several other clinical conditions. For musculoskeletal diseases, we found three trials that used interventions with no common features. Myocardial infarction, glaucoma, and multiple sclerosis had just one trial each. We found no eligible studies for cancer; likely reasons include the restrictions specified for this review to patient-administered medications and to outpatient settings. We found no eligible studies that explicitly focused on patients with adherence problems related to polypharmacy, although a few studies included patients with two or more conditions and assessed adherence to more than one medication.

Collectively, the most consistent evidence was that various types of interventions improved medication adherence outcomes for hypertension, heart failure, depression, and asthma. These improvements were accompanied by improvements in systolic and diastolic blood pressure for case management and face-to-face education with pharmacists for hypertension; reduced emergency department visits and improved patient satisfaction for pharmacist-led multicomponent interventions for heart failure; improved symptoms, pulmonary function, health care utilization, and quality of life for shared decisionmaking for asthma patients; improved symptoms for case management for depression; and improved symptoms and patient satisfaction with medications and quality of care for collaborative care for depression

We generally graded these interventions as beneficial with low to moderate strength of evidence, depending on the specific type of intervention. Of note, three clinical conditions (hypertension, heart failure, and depression) included some interventions for which evidence was insufficient due to lack of consistency or precision in the evidence (Table C).

Table B. Summary of results for patient, provider, and systems interventions (KQ 1)

Clinical Condition	Type of Intervention	Strength of Evidence for Medication Adherence	Number of Studies; n of Individuals (n Analyzed); Results	Strength of Evidence for Other Outcomes	Number of Studies; n of Individuals (n Analyzed); Results
Diabetes	Case management/ collaborative care[33-35]	Low SOE of benefit for medication adherence	3; 507 (507) Varied measures and magnitude	Low SOE of benefit for HbA1C	1; 58 (58) 1.2 percentage points difference
	Education with social support[36]	Insufficient for medication adherence	1; 199 (189) No stat sig difference	NA	NA
	Health coaching[37]	Insufficient for medication adherence	1; 56 (49) No stat sig difference	NA	NA
Hyperlipidemia	Collaborative care[35]	Insufficient for medication adherence	1; 329 (117 on lipid-lowering meds) No stat sig difference	NA	NA
	Decision aids[38-40]	Insufficient for medication adherence	2; 248 (98 + NR in 1 trial) Variable self-report measures with variable outcomes	Low SOE of benefit for patient satisfaction	1; 98 (98) Variable self-report measures, some improvements for intervention group in specific areas
	Education and behavioral support (telephone or mail)[41-45]	Low SOE of benefit for medication adherence	5; 18,492 (9,411 + NR in 1 trial) Variable measures (self-report, pharmacy refill) with variable outcomes	NA	NA
	Multicomponent (education face-to-face with pharmacist + blister packaging)[46]	Insufficient for medication adherence	1; 159 (159) Improved in intervention group over 6 months; outcome at risk of bias due to differing measurement frequency: (1) Percentage adherence (95.5% vs. 69.1%) (2) Percentage with ≥80% adherence (97.4 vs. 21.7)	Insufficient for LDL-C	1; 159 (135) No stat sig difference between groups

Table B. Summary of results for patient, provider, and systems interventions (KQ 1) (continued)

Clinical Condition	Type of Intervention	Strength of Evidence for Medication Adherence	Number of Studies; n of Individuals (n Analyzed); Results	Strength of Evidence for Other Outcomes	Number of Studies; n of Individuals (n Analyzed); Results
Hypertension	Blister packaging[47]	Low SOE of benefit for medication adherence and persistence	1; 93 (85) MPR: 6 percentage points difference between groups Percentage of patients who had prescriptions refilled on time: 14.3 percentage points difference between groups	Insufficient for SBP + DBP; angina, MI, or stroke	1; 93 (85) No stat sig difference in change in SBP or DBP or in percentage of patients with reduced SBP, angina, MI, or stroke 29.8 percentage points difference in patients with reduced DBP at 12 months in intervention group
				Insufficient for health care utilization: ED visits + hospitalizations	1; 93 (85) No stat sig difference between groups for either outcome
	Case management[48-50]	Low SOE of benefit for medication adherence	3; 516 (64 + NR in 2 studies) Two of 3 RCTs with stat sig difference in adherence: (1) MEMS ≥80% adherence: 46.8 percentage points more in experimental than control group (2) MEMS adherence, mean: 11.3 percentage points higher in experimental group	Low SOE of benefit for SBP + DBP	2; 214 (64 + NR in 1 study) Difference in SBP: - 8.5 to -14 mm Hg (range across studies) Difference in DBP: -3.1 to -9.2 mm Hg (range across studies)
	Collaborative care[35,51,52]	Low SOE of no benefit for medication adherence	3; 1,194 (785) No stat sig differences between groups	NA	NA
	Education (face-to-face with pharmacist)[46,53-55]	Low SOE of benefit for medication adherence; insufficient for persistence	3; 348 (344) for adherence Variable outcomes for adherence, some stat sig differences favoring intervention 1; 56 (53) for refilling meds on time No stat sig difference between groups refilling meds on time	Moderate SOE of benefit for SBP	2; 292 (268) -6.4 or -8.9 mm Hg mean SBP difference
				Insufficient	2; 292 (268) 1.1 or -4.4 mm Hg mean DBP difference
				Insufficient for quality of life	1, 133 (NR) No stat sig differences for sexual dysfunction, dizziness, and headaches
				Low SOE of benefit for patient satisfaction	1; 133 (130) Stat sig improvement in 4 of 5 questions

Table B. Summary of results for patient, provider, and systems interventions (KQ 1) (continued)

Clinical Condition	Type of Intervention	Strength of Evidence for Medication Adherence	Number of Studies; n of Individuals (n Analyzed); Results	Strength of Evidence for Other Outcomes	Number of Studies; n of Individuals (n Analyzed); Results
				Low SOE of benefit for hospital visits	1; 133 (124) 0.08 fewer hospital visits in intervention group
				Low SOE of benefit for contact withother health care providers	1; 133 (124) 0.41 fewer visits in intervention group
				Insufficient for ED visits	1; 133 (124) No stat sig difference
Hypertension (continued)	Education and behavioral support (telephone, mail, and/or video)[43,56-60]	Low SOE of benefit for medication adherence	5; 6,996 (5,149 + NR in 2 studies) Multiple variable outcomes Two RCTs with stat sig difference in adherence showing 6 percentage points higher in intervention group from baseline to 6 months and greater adherence at 12 and 18 months; no numbers reported	Insufficient for SBP or DBP	1; 299 (267) No stat sig difference between groups in change from baseline to 6 months
	Education with social support[36]	Insufficient for medication adherence	1; 199 (199) No stat sig differences between groups at 12 months	NA	NA
	Risk communication[61]	Insufficient for medication adherence	1; 89 (89) No stat sig difference between groups at 3 months	NA	NA
Heart Failure	Patient access to medical records[62]	Insufficient for medication adherence	1; 107 (NR) No stat sig difference at 6 or 12 months	NA	NA

Table B. Summary of results for patient, provider, and systems interventions (KQ 1) (continued)

Clinical Condition	Type of Intervention	Strength of Evidence for Medication Adherence	Number of Studies; n of Individuals (n Analyzed); Results	Strength of Evidence for Other Outcomes	Number of Studies; n of Individuals (n Analyzed); Results
Heart Failure	Case management[63]	Low SOE of benefit for medication adherence	1; 156 (156) Difference in percentage points for med adherence: 6.6 to 6.8 (range) Difference in percentage points for proportion with >80% adherence between groups: 15.7 to 16.3	Insufficient for all-cause hospital admission	1; 156 (156) No significant difference in multiple measures of all-cause readmission
	Multicomponent pharmacist led[64]	Low SOE of benefit for medication adherence	1; 314 (314 for MEMS NR for MPR or self-report) 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 for MPR over 12 months: 4.2 No stat sig difference for self-report	Insufficient for quality of life	1; 314 (NR) No stat sig difference
				Low SOE of benefit for patient satisfaction	1; 314 (NR) Difference of 0.3 on 12-point validated questionnaire
				Low SOE of benefit for all-cause ED visits and all-cause ED + hosp	1; 314 (314) Difference of 0.52 mean all-cause ED visits and 0.69 mean all-cause ED + hosp between groups
				Insufficient for health care utilization, including all-cause hospitalization, CV-related and HF-related events, costs	1; 314 (314) No stat sig difference
	Reminder video and telephone calls[65]	Low SOE of benefit for medication adherence	1; 60 (50) Difference of 17% to 27% comparing video and telephone to control in MEMS adherence over 8 weeks	Insufficient for quality of life	1; 60 (42) No stat sig difference

Table B. Summary of results for patient, provider, and systems interventions (KQ 1) (continued)

Clinical Condition	Type of Intervention	Strength of Evidence for Medication Adherence	Number of Studies; n of Individuals (n Analyzed); Results	Strength of Evidence for Other Outcomes	Number of Studies; n of Individuals (n Analyzed); Results
Myocardial Infarction	Education and behavioral support[66]	Low SOE of benefit for medication adherence; insufficient for persistence	1; 907 (836) Percentage points mean increase in adherence over 9 months: 4.3 Percentage points difference with ≥80% adherence: 6 No stat sig difference for persistence	NA	NA
Asthma	Self-management[67-71]	Moderate SOE of short-term benefit in medication adherence	Difference in percentage points for adherence: 14 to 31	Insufficient for pulmonary function and inflammation markers	2; 152 (149) No stat sig difference
				Insufficient for symptom improvement	5; 303 (300) Varied measures and magnitude (inconsistent)
				Low SOE of no benefit for quality of life	4; 248 (245) Varied measures and magnitude (consistent)
	Shared or clinical decisionmaking[72]	Low SOE of benefit for medication adherence	1; 612 (612) Difference in medication acquisition ratio for all asthma medications: 0.13 to 0.21	Low SOE of benefit for pulmonary function	1; 612 (612) Difference in FEV1 percentage points: 2.7 to 3.4
				Low SOE of benefit for symptom improvement	1; 612 (612) Difference in mean equivalents of SABA canister equivalents acquired at 2 years between shared decisionmaking and usual care: 1.6
				Low SOE of benefit for quality of life	1; 612 (612) Difference in subscale scores on 5-item Mini Asthma Quality of Life Questionnaire: 0.3-0.4
				Low SOE of benefit for health care utilization	1; 612 (612) Difference of 0.3 to 0.4 fewer asthma-related visits per year

Table B. Summary of results for patient, provider, and systems interventions (KQ 1) (continued)

Clinical Condition	Type of Intervention	Strength of Evidence for Medication Adherence	Number of Studies; n of Individuals (n Analyzed); Results	Strength of Evidence for Other Outcomes	Number of Studies; n of Individuals (n Analyzed); Results
Asthma or COPD	Pharmacist or physician access to patient adherence information[73,74]	Low SOE of no benefit for medication adherence	2; 3,811 (3,596) No stat sig difference	NA	NA
Depression	Case management[33,48,75-77]	Moderate SOE of benefit for medication adherence	3; 508 (437) Difference in percentage points for adherence or filling prescriptions over time: 9 to 15 (range across studies)	Moderate SOE of benefit for symptom improvement	3; 508 (437) Difference in CES-D scale: 7.0 to 9.4 (range across studies) Mean difference in SCL-20 (0 to 4 range) scores between groups across 12 months: 0.08
				Insufficient for self-reported disability	1; 386 (315) Varied measures, outcomes, time periods
	Collaborative care[78-83]	Moderate SOE of benefit for medication adherence for telephone + in person; insufficient for telephone only; insufficient for depression + HIV patients	3 (telephone and in person); 598 (598) Difference in percentage points for adherence: 16.5 to 40.3 (range across studies) No stat sig difference for depression + HIV patients or telephone collaborative care only	Low SOE of benefit for symptom improvement for major depression or moderate depression; insufficient for severe or minor depression	Severe depression: 2; 214 (214) Minor depression: 1; 149 (149) Moderate depression: 2; 156 (156) Major depression: 1; 79 (79) Varied measures, outcomes, time periods
				Low SOE of benefit for patient satisfaction with antidepressants	2; 370 (370) Difference in percentage points in those rating antidepressants as helping somewhat to a great deal: 6.0 to 24.8 (range across studies)
				Insufficient for health care utilization	3; 598 (598) Varied outcomes, time periods, and consistency
				Insufficient for costs	1; 228 (228) No stat sig difference

Table B. Summary of results for patient, provider, and systems interventions (KQ 1) (continued)

Clinical Condition	Type of Intervention	Strength of Evidence for Medication Adherence	Number of Studies; n of Individuals (n Analyzed); Results	Strength of Evidence for Other Outcomes	Number of Studies; n of Individuals (n Analyzed); Results
				Moderate SOE of benefit for patient satisfaction with quality of care	3; 598 (598) Difference in percentage points in those rating quality of care as good to excellent: 5.1 to 32.5 (range across studies) at 3 to 4 months, 16 at 6 months
Depression (continued)	Medication telemonitoring or telephone care[84,85]	Insufficient for medication adherence	2; 270 (255) No stat sig difference	NA	NA
	Reminders to nonadherent patients and lists of nonadherent patients to providers[86]	Low SOE of benefit for medication adherence	1; 9,564 (9,564) Difference in percentage points for adherence: 1 to 3 (range across study)	NA	NA
Glaucoma	Multicomponent intervention[87]	Low SOE of benefit for medication adherence	1; 66 (66) Difference in adherence rate: 0.22	Insufficient for intraocular pressure	1; 66 (66) No stat sig difference
Multiple Sclerosis	Counseling (software-based telephone)[88]	Low SOE of benefit for medication adherence	1; 435 (367) Difference in percentage points of patients who discontinued use of multiple sclerosis therapy: 7.5	NA	NA
Musculoskeletal Diseases	Decision aid[89]	Insufficient for medication adherence, persistence, initiation of therapy	1; 100 (100) Varied outcomes and measures	Insufficient for patient satisfaction	1; 100 (NR) No stat sig difference
	Case management[90]	Insufficient for medication adherence	1; 127 (127) No stat sig difference	NA	NA
	Virtual osteoporosis clinic[91]	Low SOE of benefit for medication adherence	1; 235 (211) Difference in percentage points of women using osteoporosis medication at 13 months: 23.7	Insufficient for patient satisfaction	1; 235 (211) No stat sig difference

Table B. Summary of results for patient, provider, and systems interventions (KQ 1) (continued)

Clinical Condition	Type of Intervention	Strength of Evidence for Medication Adherence	Number of Studies; n of Individuals (n Analyzed); Results	Strength of Evidence for Other Outcomes	Number of Studies; n of Individuals (n Analyzed); Results
Multiple or Unspecified Chronic Conditions	Case management intervention[92-94]	Low SOE of no benefit for persistence	3; 3,307 (3,269) No stat sig difference	NA	NA
	Outreach, education, and problem-solving (pharmacist led)[95]	Insufficient for medication adherence	1; 96 (75) No stat sig difference	NA	NA

Abbreviations: CES-D scale = Center for Epidemiologic Studies-Depression scale; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; DBP = diastolic blood pressure; ED = emergency department; FEV1 = forced expiratory volume at 1 minute; G = group; HF = heart failure; HbA1c = hemoglobin A1c; hosp = hospitalization; KQ = Key Question; LDL-C = low-density lipoprotein cholesterol; MEMS = medication event monitoring system; MI = myocardial infarction; MPR = medication possession ratio; NA = not applicable; NR = not reported; RCT = randomized controlled trial; SABA = short-acting beta agonists; SBP = systolic blood pressure; SCL-20 = Hopkins Symptom Checklist-20; SOE = strength of evidence; stat sig = statistically significant.

Table C. Summary of strength-of-evidence grades for medication adherence by type of intervention

Type of Intervention	Diabetes	Hyper-lipidemia	Hyper-tension	Heart Failure	Myocardial Infarction	Asthma	Depression	Glau-coma	MS	Musculo-skeletal Diseases	Multiple or Unspeci-fied Conditions
Blister packaging			MA: L(+) Pers: L(+)								
Case management	MA: L(+)		MA: L(+)	MA: L(+)			MA: M(+)			MA: INS	Pers: L(-)
Collaborative care (telephone + in person)	MA: L(+)	MA: INS	MA: L(-)				MA: M(+)				
Collaborative care (telephone only)							MA: INS				
Counseling (software-based telephone)									MA: L(+)		
Decision aids		MA: INS								MA, pers, init: INS	
Education (face-to-face with pharmacist)			MA: L(+) Pers: INS								
Education + behavioral support (telephone, mail, and/or video)		MA: L(+)	MA: L(+)		MA: L(+) Pers: INS						
Education + social support	MA: INS		MA: INS								
Health coaching	MA: INS										
Multicomponent interventions		MA: INS		MA: L(+)				MA: L(+)			
Outreach, education, and problem-solving											MA: INS
Patient access to medical records				MA: INS							
Pharmacist or physician access to patient adherence data						MA: L(-)					
Reminders				MA: L(+)			MA: L(+)				
Risk communication			MA: INS								
Self-management						MA: M(+)					
Shared or clinical decisionmaking						MA: L(+)					
Telemonitoring							MA: INS				
Virtual clinic										MA: L(+)	

Abbreviations: init = initiation of therapy; INS = insufficient; L(-) = low strength of evidence of no benefit; L(+) = low strength of evidence of benefit; M(+) = moderate strength of evidence of benefit; MA = medication adherence; MS = multiple sclerosis; pers = persistence.

For asthma and hypertension, because of several studies of low or moderate risk of bias that failed to find an effect, we judged that two interventions provided evidence of no benefit: these two interventions included collaborative care for hypertension and patient or provider access to patient adherence data for asthma.

Trials in diabetes, hyperlipidemia, and musculoskeletal diseases found a single intervention indicating benefit for medication adherence. These trials focused on care coordination and collaborative care approaches for diabetes, education and behavioral support for hyperlipidemia, and a virtual clinic for osteoporosis. All other approaches failed to produce improvements and were judged to be insufficient for lack of consistency or lack of precision in the results.

The least consistent evidence of improvement in medication adherence pertained to patients with multiple chronic conditions: three trials, using pharmacist-based outreach, education, and problem-solving approaches, provided evidence of no benefit for medication adherence, and findings from another trial, using case management, were insufficient.

We found the least evidence for myocardial infarction, glaucoma, and multiple sclerosis. Single trials in each of these clinical areas suggested low strength of evidence of benefit for medication adherence.

Findings Specific to Interventions

We identified 20 intervention approaches (Table C) across the clinical conditions included in this comparative effectiveness review. Intervention approaches tested in patient populations with different clinical conditions (either single diagnoses of chronic illnesses or, in some cases, two or more such ailments) included case management, collaborative care, decision aids, education, reminders, and pharmacist-led multicomponent approaches. Our findings suggest that educational interventions and case management approaches offer the most consistent and voluminous evidence of improvements in medication adherence across varied clinical conditions. We found moderate strength of evidence for self-management interventions for asthma, which generally include strong educational components. Trials showing improvement with case management and educational interventions provided some evidence of improvement for other health outcomes. We found low strength of evidence of benefit from educational interventions for medication adherence for hypertension, hyperlipidemia, and myocardial infarction, and insufficient evidence for diabetes. We found low or moderate strength of evidence of benefit from case management for diabetes, hypertension, heart failure, and depression; insufficient evidence for musculoskeletal diseases; and low strength of evidence of no benefit for persistence for multiple chronic conditions.

Other promising approaches tested and found to be effective in more than one clinical area include reminders and pharmacist-led multicomponent approaches. Interventions such as shared decisionmaking and blister packaging were tested in a single clinical area with a single trial; without additional evidence, their widespread applicability is difficult to judge but may well hold promise. Some interventions may be most effective for a particular clinical condition. Collaborative care appeared to be effective primarily for patients with depression or with depression and diabetes; for other clinical conditions (hyperlipidemia and hypertension), the evidence was insufficient.

The categories noted above are shorthand for one or more key elements of very diverse interventions. As explained earlier, we opted not to try to impose any external taxonomy on these markedly different programs; none seemed suitable for capturing the underlying constructs or specific activities we encountered in this literature. 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, whereas the other did not. Thus, the inductive approach we used to identify types of interventions allowed us to group them in ways that seemed to reflect key similarities, but doing so limited our ability to draw firm conclusions about the effectiveness of *specific* intervention features. In addition, the trials that tested multicomponent efforts did not have multiple intervention arms that would have provided information about individual elements of the intervention effort. Nevertheless, we attempted to address this limitation through analyses for KQ 3, and those findings offer further insights on some common elements across these interventions.

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

Five studies[96-100] evaluated the effects of policy-level interventions on medication adherence, specifically for cardiovascular disease, diabetes, and respiratory conditions (Table D). One study was an RCT. The other four studies used cohort designs. All of the studies 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 comparison of results.

All five 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.[96] This study found a large improvement in adherence among individuals who had had no prescription drug coverage before 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.

All five policy-level studies found statistically significant between-group differences in adherence to medications used to treat cardiovascular conditions favoring the group that had out-of-pocket expenses reduced. However, we find these differences somewhat difficult to interpret because medication adherence decreased over time in all groups in two of the studies that used cohort designs. Nonetheless, the magnitude of effects observed in the cohort studies were similar to those reported in the RCT.[97] Therefore, we concluded that evidence of moderate strength indicates 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.

Three policy-level studies found statistically significant between-group differences in adherence to medications used to treat diabetes favoring the group that had out-of-pocket expenses reduced. As above, we find these differences somewhat difficult to interpret because all of these studies used cohort designs and medication adherence decreased over time in all groups in two of the studies. Nonetheless, the magnitude of effects observed in these two studies were similar to those in the Medicare Part D study among individuals who had had some prescription drug coverage before Medicare Part D but whose out-of-pocket medication expenses following its implementation dropped.[96] Therefore, we concluded that evidence of moderate strength indicates that policy-level interventions that reduce patient out-of-pocket expenses can have a beneficial effect on adherence to medications used to treat diabetes.

Table D. Summary of evidence for policy-level interventions (KQ 2)

Clinical Condition	Intervention	Comparator	Number of Studies	Medication Adherence	Other Outcomes
Cardiovascular disease[96-100]	Improved prescription drug coverage[a]	Unchanged prescription drug coverage	5	Benefit: moderate SOE	Insufficient SOE
Diabetes[96,98,100]	Improved prescription drug coverage[a]	Unchanged prescription drug coverage	3	Benefit: moderate SOE	No evidence
Inhaled corticosteroids[b,98]	Reduced medication copay	Unchanged medication copay	1	Insufficient SOE	No evidence

[a]Includes all policy-level interventions that reduced patient out-of-pocket expenses for prescription drugs.
[b]Inhaled corticosteroids are usually used to treat reactive airway disease conditions such as asthma and chronic obstructive pulmonary disease.
Abbreviations: KQ = Key Question; SOE = strength of evidence.

One study found no effect of a policy-level intervention on adherence to inhaled corticosteroids, usually used to treat reactive airway disease conditions. Therefore, we concluded that evidence is insufficient to draw conclusions for the effectiveness of policy-level interventions in this clinical area.

One study examined the effect of policy-level interventions on clinical outcomes.[97] This study found a 14-percent reduction in the rate of first vascular events following hospital discharge for a myocardial infarction. The same study found a 26-percent reduction in total patient spending but no change in total insurer paying. We concluded that evidence is insufficient to draw conclusions regarding the effects of policy-level interventions on clinical and economic outcomes.

KQ 3a: Characteristics of Medication Adherence

Overall, the extreme heterogeneity of terminology used to describe medication adherence interventions in the studies reviewed hindered our ability to compare effects of different features of the interventions across studies and across diseases. The diversity of the interventions themselves made identification of "intervention type" clusters challenging.

Most, but not all, studies provided information, although not in any standardized manner, about six key intervention characteristics: 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 more than 50 percent of the interventions aimed at various combinations 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 identified some general patterns of combinations of the six features. For example, interventions varied in the number of contacts they entailed from 1 to 30, but those with more contacts tended to involve telephone contact. Similarly, certain intervention components, such as facilitation and knowledge-based components affecting the delivery of medical information, were commonly used across most interventions. In contrast, 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 programs than among either pharmacist- or physician-delivered interventions. The specific components of the interventions were the least well-characterized aspect of this literature,

although it was often these components that most meaningfully distinguished the interventions from one another. 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. Very few studies directly compared one feature of an intervention with another feature to determine which aspects of the intervention had the most effect on outcomes. A longstanding debate exists about the advantages and disadvantages of testing multicomponent interventions, which may increase the likelihood of having an impact, versus those of testing each component in isolation to understand its individual effects. Researchers may first combine approaches to document an effect and in later studies "peel away the layers of the onion" to isolate relative effects of separate components. The paucity of this second type of study design may reflect the state of the field. As studies increasingly demonstrate efficacious combination interventions, in the future we may see more studies that attempt to isolate effects of intervention features. Among the four studies that did conduct this kind of comparison, each compared *different* aspects of *different* interventions.

As a result, we could not pool data across even these four studies. One demonstrated that shared decisionmaking (in which nonphysician clinicians and patients negotiated a treatment regimen that accommodated patient goals and preferences) had a greater effect on adherence to asthma medications than did a clinical decisionmaking approach (in which the physician prescribed the treatment without specifically eliciting patient goals or preferences). Both approaches were more efficacious than usual care. The effects of shared decisionmaking on adherence lasted up to 2 years, whereas those attributed to clinical decisionmaking had attenuated at that point. Another study, conducted among patients with heart failure, directly compared two different delivery modes of the same information (telephone vs. videophone). This study found no difference between the two delivery modes regarding improvement in adherence, but both were superior to usual care. Another study directly compared the agent of delivery (physician vs. research staff) using the same mode (face-to-face contact) to deliver a decision aid among patients with diabetes to try to help them decide whether to take statins to lower their risk of cardiovascular disease. Patients who were given the decision aid had better adherence than those receiving usual care, regardless of who delivered the aid.

We conclude that mode of delivery was an important feature only in certain settings. However, incorporation of patient preferences through shared decisionmaking about treatment seems more efficacious at improving and sustaining improvement in asthma medication adherence than traditional clinical decisionmaking that does not take into account patient preferences in selecting a recommended treatment. Shared decisionmaking appeared to improve pulmonary function tests when compared with clinical decisionmaking, but this approach did not improve quality of life or health care utilization; we rated this evidence as having low strength (Table E).

Table E. 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[72]	Shared decisionmaking	Clinician decisionmaking	1	Benefit: low SOE	No evidence	Benefit: low SOE	Insufficient	No benefit: low SOE	No benefit: low SOE
Heart failure[65]	Telephone reminders	Video reminders	1	Insufficient	No evidence	No evidence	No evidence	No evidence	No evidence
Diabetes[39]	Decision aids delivered by clinician	Decision aids delivered by research staff	1	Insufficient	No evidence	No evidence	No evidence	No evidence	No evidence
Multiple chronic conditions[50]	Nurse case management with telemonitoring and high-intensity education	Nurse case management with telemonitoring and low-intensity education	1	Insufficient	No evidence	Not applicable	No evidence	No evidence	No evidence

Abbreviation: SOE = strength of evidence.

KQ 4: Outcomes for Vulnerable Populations

We searched for evidence on a broad set of vulnerable populations. For certain vulnerable subgroups—specifically for patients with major depression, severe depression, or depression and coexisting hypertension; Black patients with depression and coexisting diabetes; and elderly patients with diabetes, hyperlipidemia, heart failure, or hypertension—we determined that interventions with a positive impact on medication adherence had only low strength of evidence. Evidence was insufficient about benefit to adherence of interventions dealing with patients who had depression with coexisting HIV, patients who had diabetes and depression (except for Black patients with diabetes and depression), patients with diabetes and hypertension, and patients from rural communities. 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 patients and 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 resulted in any unintended negative 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 great that we determined that the evidence was insufficient to reach definitive conclusions.

Discussion

Key Findings and Strength of Evidence

We found evidence of effective interventions to improve medication adherence for many chronic conditions. These analyses suggest that patients' adherence to chronic-disease medications can be improved through programs targeting patients, providers, health systems, or policy. They demonstrated that a broad range of approaches can work.

Adherence is typically the result of a combination of patient, provider, and policy factors. Indeed, most of the 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, no single "silver bullet" exists for medication adherence.

We found the strongest evidence for enhancing adherence with reduced copays across clinical conditions, self-management of asthma (for short-term outcomes), and collaborative care or case management for depression. Within clinical conditions, we found the strongest evidence for depression case management for depression symptom improvement and pharmacist-led hypertension approaches for systolic blood pressure improvement. We found consistent evidence or evidence from more than one clinical area supporting medication adherence interventions such as education, reminders, and pharmacist-led multicomponent interventions.

Clinicians and policymakers should keep in mind that we found very little evidence of any relationship between medication adherence and adverse events, although what we found suggests that improving adherence did not increase the incidence of adverse events. However, many of the conditions studied did not involve medications typically associated with very severe common side effects. This review is the first we are aware of that systematically reviewed information on adverse events. It thus provides information that should be confirmed in future studies and reviews.

The lack of studies evaluating potential mechanisms that link improved adherence with other health-related or health services outcomes somewhat constrains policymakers' and clinicians' options. We did not find evidence of studies among patients with chronic illnesses that tend to have more intermittent disease trajectories, such as certain types of arthritis, diverticulitis, and other gastrointestinal conditions. In particular, decisionmakers should exercise caution in trying to use any a la carte approach to implementing components of complex interventions to enhance patients' medication adherence. We do not think that sufficient information is yet available to guide choices among the considerable array of program components, especially to pick and choose only some parts of multicomponent approaches. Therefore, future studies must 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. Meanwhile, however, if studies have not been done in their specific clinical patient population, clinicians and health system administrators may want to give more thought to how they might be able to extrapolate existing results to their specific patient populations—that is, take apparently successful programs and apply them to groups with diagnoses and other characteristics similar to those in the successful program. For example, interventions similar to those that were successful at improving adherence to medication for hypertension and hyperlipidemia may help in other settings in which the illness is asymptomatic and medication is taken primarily to prevent long-term complications.

Poor medication adherence is known to result in large downstream health care costs. An important finding for policymakers contemplating changes in health policy is our assessment of moderate-strength evidence from five consistent studies that reducing patients' out-of-pocket costs or improving prescription drug coverage 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 analyzed in this review were not highly selective; rather, they ranged from relatively minimalist to complex and intense, although evidence often came from small studies. Neither were these studies limited to narrow or unrepresentative disorders or disease severity; rather, they reflected studies done across a substantial variety of chronic conditions affecting adults. Thus, in one sense the evidence from this review might be regarded as relatively applicable across numerous different options for health care providers to pursue for their adult patients with major chronic diseases or multiple chronic conditions. Our findings are not generalizable to children or young adolescents because of our inclusion criteria.

As noted, many of our findings came from single, often small or short-term, trials, some with important questions about risk of bias. Findings from this diversity of clinical conditions and interventions have not yet been replicated in trials in larger patient populations, in groups drawn from different settings and with different sociodemographic characteristics, or in investigations with longer observation and followup periods. These gaps in the evidence base constrain somewhat the applicability of our results.

Another limitation to the applicability of this evidence comes from the complexity of multicomponent interventions. Studies did not generally provide information on how researchers identified the separate active components in their interventions or how they had operationalized

those components; generally, these complex programs lacked detailed instructions and users' manuals by which other groups might try to replicate the original research.

Finally, the degree to which these interventions require fidelity to protocol when being implemented in other settings or through different study designs (e.g., nonexperimental studies) is unclear. The need for fidelity to protocol or the allowable appropriate adjustments for other patient populations (e.g., different illnesses, different sociodemographic characteristics) are likely a matter of some debate. These questions place some limits on the wide applicability of the evidence reported here.

Limitations

The constraints for population and setting we imposed on the systematic review limit the applicability of this review, as discussed above. We did not review the evidence on populations with HIV/AIDS, mania, bipolar disorder, or substance abuse. We excluded studies among patients with HIV/AIDS because existing comprehensive reviews of these interventions had been conducted recently. We also excluded studies of acute conditions, severe mental illness, and substance abuse to improve our ability to potentially pool findings, since adherence for short-term acute conditions and those involving addictions or cognitive limitations is different from adherence for chronic medications. However, interventions for these excluded clinical conditions may have applicability to the conditions that we included in our review. We limited this review to adults and cannot, therefore, address important adherence concerns for children and adolescents with chronic conditions such as type 2 diabetes. Another limitation is geographic location: we excluded non-English and non-U.S. studies. This criterion may well have decreased the pool of eligible studies we might have examined, but the applicability of those studies to the United States is unclear. Our approach to categorizing interventions for KQ 1 relied essentially on the short descriptions in published manuscripts; their similarities or differences were substituted for any overarching taxonomy, as none that we considered seemed to fit our purpose. Thus, we have introduced intervention labels that, admittedly, do not fully describe or account for heterogeneity within and across clinical conditions or patient populations. This approach limits our ability to make definitive statements about the effectiveness of interventions across clinical areas; we believe the clusters and categorizations we used are useful heuristics, but they may be regarded more as hypothesis generating than as reflecting settled principles of classification. Our pool of included interventions is limited to those that were designed specifically to address medication adherence as a primary or secondary outcome. Finally, we did not include clinical trials of drugs that considered adherence as a component of safety and efficacy; as a result, we do not address the effectiveness of specific drug formulations that may improve adherence by limiting adverse effects.

Research Gaps

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 our ability to pool results from studies. If investigators could use more standardized objective adherence outcomes in future research, their results might be more easily analyzed and interpreted 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 we could safely draw about the efficacy of specific intervention features. Although 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.

Most trials were not placed in a larger context of improving the quality of health care delivered; only a minority examined issues such as quality of life and patient-reported outcomes or patient satisfaction. This limitation interacts with the issues noted above about understanding the effectiveness of these programs, not simply their efficacy, which is especially important for providing information suitable for broadly based clinical and policy decisionmaking. At a minimum, using guidelines from the Standards for Quality Improvement Reporting Excellence (SQUIRE) group (http://squire-statement.org/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.[101]

Finally, although many studies assessed some health outcomes, these often were not reported by patients themselves, and many were relatively short term (at least in the context of lifelong chronic ailments). Including long-term health outcomes and mounting efforts to solicit information directly from patients in future trials or observational studies of adherence would enhance the Nation's capacity to assess the overall significance of adherence interventions. While the minimum length of followup indicated may vary by condition, for lifelong chronic ailments, medication adherence often decays over at least the first year. Hence, studies that follow patients longer than 1 year could provide information about adherence levels once they have reached a plateau. Collecting information about costs will be crucial, because no health systems or facilities can afford to try all approaches across the diverse patient populations they serve. Economic information is essential in and of itself, but it will also facilitate cost-effectiveness analyses of such interventions.

Conclusions

Despite the heterogeneity of adherence measurement, interventions tested, and characterization of interventions, we found the most consistent evidence of improvement in medication adherence for policy-level interventions to reduce out-of-pocket expenses, case management, and educational interventions across clinical conditions. Within clinical conditions, we found the strongest support for self-management of medications for short-term improvement in adherence for asthma patients; collaborative care or case management programs for short-term improvement of adherence and symptom improvement for patients taking depression medications; and pharmacist-led approaches for hypertensive patients to improve systolic blood pressure.

We found low strength of evidence for many other interventions; these diverse groups of approaches offer promise but require more research to establish their value (or lack of it). Far less evidence was available to show whether most of these interventions improved patients' health outcomes, given better adherence to their medication regimens. Several reviews that researchers have conducted over the past two decades—now complemented by our review—confirm that medication adherence can be improved via formal programs of various sorts. 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 both the quality and the effectiveness of health care for all Americans requires both knowledge and tools. Although medical researchers have demonstrated that many efficacious medical treatments can 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 treatment, however, provides an additional explanation for the discontinuity between recommended treatment and actual treatment outcomes. Of particular concern is adherence to recommendations about medications.

Defining Medication Adherence

Medication adherence 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 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]

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] Health outcomes may be improved by helping patients better adhere to and persist with recommended treatment, in much the same sense that such outcomes may be improved by enhancing provider implementation of best practice guidelines.[7-9]

Linking Poor Medication Adherence and Health Outcomes

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, 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.[15,16]

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] To reduce the gap between potential and actual health care quality, this problem must be addressed directly.

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 calls for using a newer chronic care model.

Medication adherence is particularly salient for several vulnerable populations of interest to the Agency for Healthcare Research and Quality (AHRQ) and the IOM; these include racial and 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 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.

Linking Medication Adherence and Clinical Practice Guidelines

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; rather, it is one among several issues typically 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]

Burden of Medication Nonadherence and Prevalence of Medication Nonadherence

Poor medication adherence is relatively 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] 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]

Effects of Nonadherence on Health Outcomes and Health Care Costs

This lack of adherence to medications is prevalent and has dramatic effects on individual and population-level health. 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—including but 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.

Nonadherence has been estimated to cost the U.S. health care system between $100 billion and $289 billion annually in direct costs.[3,19,37-40] In one study, 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.[41] 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.[42-48]

Causes of Medication Nonadherence

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 four levels can lead to medication nonadherence or foster better adherence: (1) ***health policies***; (2) ***the health system;***[32] **(**3) ***health care provider****;* and (4) ***the patient.*** Many studies have examined the multiple factors associated with medication adherence.

Health policies support health care systems and influence broader societal factors that affect the patient's ability to adhere to medication recommendations; these include 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. 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 affect 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, the health system and ***health provider*** factors related to nonadherence include many potential problems. Examples include 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; this approach to clinical care 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.

Many ***patient factors*** underlie nonadherence. 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.[49-51] Substance abuse, depression,[8,49,52,53] lack of medical insurance, competing demands on time, and an erratic daily routine can all impede optimal medication use.[18,49] The factors that most influence adherence differ across individuals.[49] Therefore, interventions to improve adherence are often multipronged and tailored. The cognitive barriers that patients with psychosis, mania, or bipolar disorder face in taking medication likely differ from those associated with other chronic conditions; for

purposes of this review, we exclude studies involving patients with psychosis, mania, and bipolar disorder.

Patients may be nonadherent in many ways. Some patients may omit doses of a medication, whereas others may take extra doses. 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 be nonadherent simply by not following instructions on how to take the medication (e.g., with or without food). Other nonadherence examples include taking drug holidays (purposefully discontinuing the medication for a period of time) or even stopping 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.[51,54,55] For example, multiple studies have documented that African-American patients are less adherent, particularly to antiretroviral treatment, than White patients and have postulated that this phenomenon may explain differences in clinical outcomes.[50,51,54,55] 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.[56]

Low health literacy may be linked to poor adherence and poor health outcomes and partly explain heath disparities. 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.[57] In a systematic review of 44 studies that assessed the relationship between health literacy and health outcomes, 16 evaluated the association between health literacy and knowledge.[58] 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.[59,60] Low literacy has been associated with greater risk of hospitalization[61,62] and poorer control of type 2 diabetes.[59,63-65] 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 medication,[66] other studies failed to replicate this finding.[49,67] A recently updated systematic review of health literacy found insufficient evidence to identify a definitive link between low health literacy and medication adherence.[68,69] This same review identified only two quasi-experimental trials of interventions to enhance adherence by addressing low health literacy.[70,71] The investigators 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.[68] Nonetheless, other studies demonstrate that patients with low literacy skills have difficulty understanding prescription warning labels and identifying their medications correctly.[72,73] 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.

Possible Improvement Strategies for Medication Nonadherence

This review seeks to synthesize evidence regarding the efficacy and effectiveness of interventions to improve adherence to medication regimens used to treat an array of 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, by telephone; with print materials, by computer, or by 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 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 any 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**: De Bruin et al. developed a taxonomy of mutually exclusive medication adherence intervention components that may or may not be present in an adherence intervention.[74] We have based our taxonomy of intervention characteristics or elements on the De Bruin approach (Table 1). An intervention may include one or more of these components or attributes.

Table 1. Components of medication adherence interventions

Component	Examples
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
Attitudes	Targets attitudes toward behavior
Self-efficacy	Modeling, practice, verbal persuasion, coping responses, graded tasks, reattribution of success/failure
Self-monitoring skills	Teaching skills in self-monitoring and self-management
Intention formation	General intention, medication schedule, goals, behavioral contract
Action control	Cues/reminders, self-persuasion, social support
Maintenance	Maintenance goals, relapse prevention
Facilitation	Ongoing 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 reward	Payment or other reward for conducting behavior
Motivational interviewing	Client-centered yet directive counseling style that facilitates behavior change through helping clients resolve ambivalence
Stress management	Methods to reduce or manage stress, such as biofeedback
Organizational learning strategies	Use of implementation toolkits or learning collaboratives
Systems change—clinical champion	Use of clinician patient advocate
Systems change--quality	Continuous quality improvement system

Practitioners developing and implementing medication adherence interventions can (and do) combine any of these key characteristics with various other characteristics. This approach generates very diverse sets of interventions; for that reason, any given intervention is most often compared only with a usual care program rather than with any other intervention.

To deal with this heterogeneity, 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 through 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 types 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. 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.

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.

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 and Key Questions

Scope of the Review

This report is part of a larger initiative, the Closing the Quality Gap: Revisiting the State of the Science (CQG) series, 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.[75] 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.[76] 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.

As described above, to improve health care quality, interventions used to improve medication adherence have been developed that address health system, health care provider, or patient 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.[7,77] 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 both individual and health systems-level interventions is important.[78]

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;[79] however, this feature has not been compared for medication adherence[80] 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 between acute disease and 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 permits us to maintain some comparability across intervention types.

The earlier Cochrane review and update did not assess the impact of health system-level or policy-level interventions on adherence.[7] In our review, we assess these types of interventions and those at the patient and provider levels. In contrast, several recent reviews and meta-analyses have assessed the impact of interventions to improve medication adherence in the context of HIV treatment,[80-82] so we excluded 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 processes that affect outcomes for adults with chronic disease. The means to this end are to identify patient-, provider-, health 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). 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; we did, however, include mild to moderate depression, which does not typically impair cognition in the same severe manner as the other mental health conditions

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] the authors included studies only if they assessed health outcomes beyond medication adherence, such as mortality or morbidity measures. Although we recognize that the 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. We reviewed the literature from 1994 onward to look at the evidence from the last search date for an early and comprehensive review.[77]

Key Questions

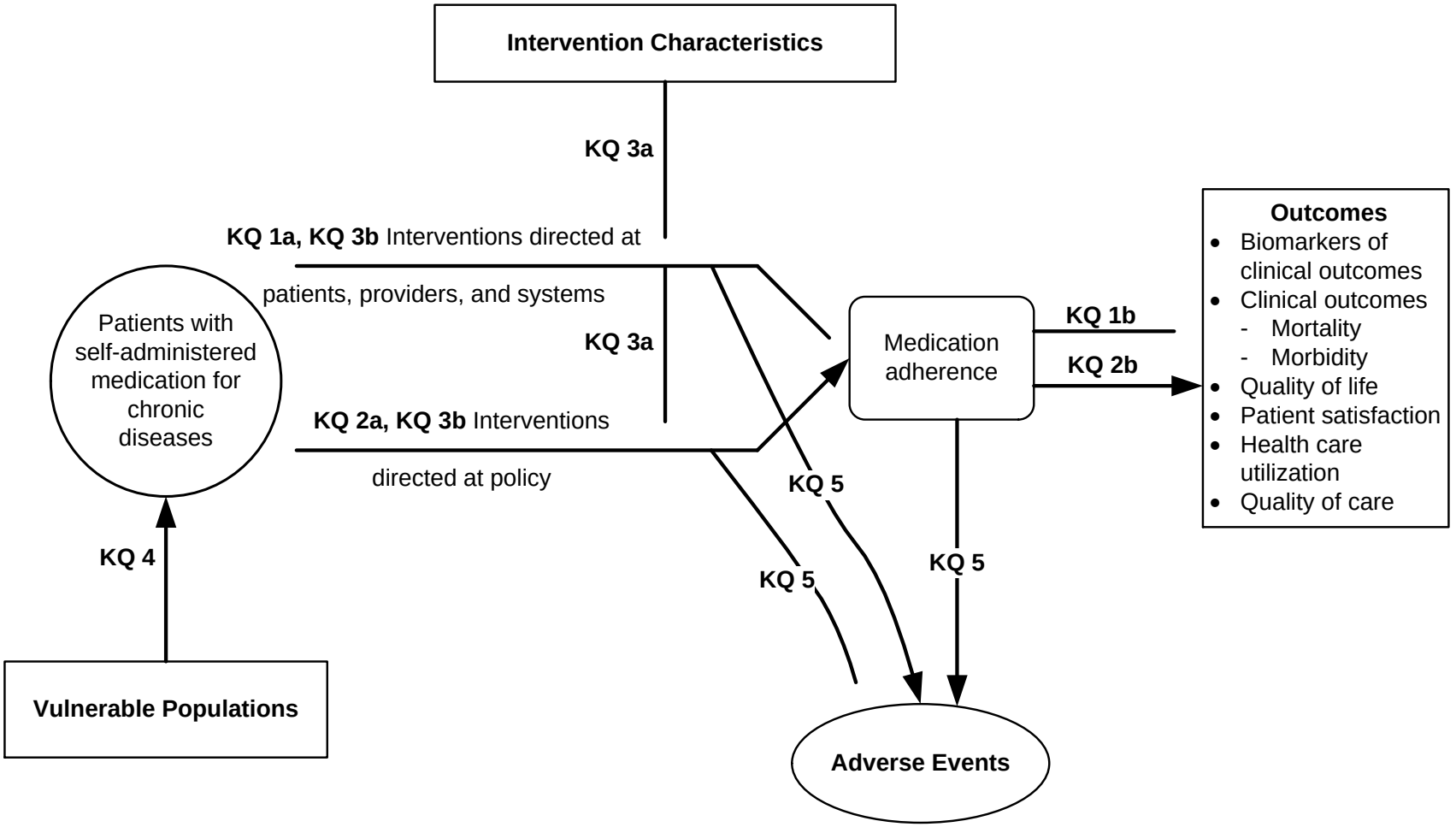
This report addresses five Key Questions (KQs), three of which have subquestions. Specifically, they are:

- 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). Because we sought to go beyond other reviews by assessing all interventions targeting medication adherence (i.e., not limited to those that 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. Analytic framework



Abbreviation: KQ = Key Question.

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 main categories of interventions.

1. 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 vs. subcutaneous)
   - Augmented pharmacy services
   - Shared decisionmaking
   - Dose-dispensing units of medication or medication charts
   - Rewards.
2. 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[74] (Table 1).

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:

1. Medication adherence
2. Other outcomes
    a. Biomarkers of clinical outcomes
    b. Clinical outcomes (mortality, morbidity measures defined by the clinical condition)
    c. Quality of life
    d. Patient satisfaction
    e. Health care utilization (including associated costs), and
    f. Quality of care
3. Adverse events.

Timing

We consider all possible lengths of interventions and followup 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), summary tables for health and other outcomes 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 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 Evidence-based Practice Center (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 clarified 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 included studies had to report both adherence and health outcomes, (2) the focus on randomized controlled trials (RCTs) alone, (3) the absence of subanalyses on vulnerable subpopulations, and (4) the lack of focus on adverse events.

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, timing, 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 TEP members 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 conducted an updated literature search (of the same databases searched initially) concurrent with the peer review process. Literature suggested by peer reviewers or from the public were investigated and, if appropriate, incorporated into the final review. Appropriateness for inclusion in the review was 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

Category	Inclusion Criteria	Exclusion Criteria
Population	• Adults prescribed self-administered medication for secondary or tertiary prevention of chronic diseases	• Children under age 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	• Outside United States
Time period	• 1994 to present	• Pre-1994
Length of followup	• No limit	

Table 2. Inclusion/exclusion criteria (continued)

Category	Inclusion Criteria	Exclusion Criteria
Settings	• Outpatient primary and specialty care settings • Community-based settings • Home-based settings	• 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 care utilization (and associated costs), quality of care for studies with a statistically significant improvement in medication adherence • Adverse events	• All other outcomes when interventions did not yield a statistically significant improvement in medication adherence
Publication language	• English	• All other languages
Admissible evidence for Key Question 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 as having 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 as having 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, interventions, comparators, settings, 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.

As specified above for 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; ITT analysis treats all participants as if they have completed the study within their treatment assignment groups, even if they have stopped participating. This type of analysis can be done by carrying forward participants' baseline observations or their last observations before study completion or attrition. 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[83] and specified in the RTI Item Bank.[84] 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 recruitment and accounting or controlling for variations in past nonadherent behavior. Selection bias occurs when comparison groups are systematically different because of nonequivalent sample recruitment methods.

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. Information bias refers to systematic error in the measurement of covariate and outcome data that leads to differences between comparison groups not caused by the intervention 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. In particular, we evaluated whether adherence measures relied solely on self-reported data. Detection bias is a type of information bias in which the measurement of outcomes is prone to error because of how they are measured.

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 for all studies with low, medium or high risk of bias (Appendix E). A list of scales used in included studies is presented in Appendix F.

Data Synthesis

We elected to stratify our results in KQ 1 by clinical condition. We based our choice of clinical condition (rather than, say intervention type) as our primary analytic lens because this approach allowed us to disentangle the possible confounding between clinical condition and type of intervention. Our analytic approach is useful for researchers working within a clinical condition. We present a brief synopsis of intervention effectiveness across clinical conditions in our discussion chapter for those clinical providers interested in the effectiveness of particular intervention approaches aimed at patients, providers, or the system.

Given the wide variation of care in the "usual care" arms of included interventions, we did not attempt indirect comparisons across interventions for KQ 1. For trials that selected patients with two concurrent clinical conditions and evaluated medication adherence and other outcomes for both conditions, we sought to reduce repetition by focusing on the outcomes specific to the medication relevant to each clinical condition. We grouped trials that selected patients with more than two concurrent clinical conditions under a section entitled "multiple chronic conditions."

KQ 2, on policy interventions, summarizes information on interventions designed to address many or all clinical conditions. We present KQ 2 by intervention type first and then provide condition-specific details. KQ 3 presents results categorized by intervention characteristics. KQ 4 presents outcomes by vulnerable subpopulation and KQ 5 presents a list of adverse events.

We specified all outcomes other than morbidity and biomarkers a priori and listed them above in the PICOTS criteria (listed in the Introduction). 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.

Grading Strength of Evidence

We graded the strength of evidence based on the guidance established for the EPC program.[85] 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 reviewed and handsearched citations from relevant systematic reviews to ensure that we included all eligible 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.

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.[85]

Applicability Assessment

We assessed the applicability of the evidence following guidance from Atkins and colleagues.[86]

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 report received external peer review. Peer Reviewers were charged with commenting on the content, structure, and format of the evidence report, providing additional relevant citations, and pointing out issues related to how we conceptualized the topic and analyzed the evidence. Our Peer Reviewers (listed in the front matter) gave us permission to acknowledge their review of the draft. In addition, the Scientific Resource Center placed the draft report on the AHRQ Web site (http://effectivehealthcare.ahrq.gov/) for public review. We compiled all peer review and public comments and addressed each one individually, revising the text as appropriate. AHRQ staff and an associate editor provided reviews. A disposition of comments from public commentary and peer review will posted on the AHRQ Effective Healthcare Web site (www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/) 3 months after the final report is posted.

Results

Introduction

This chapter 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 [KQ 3a] 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

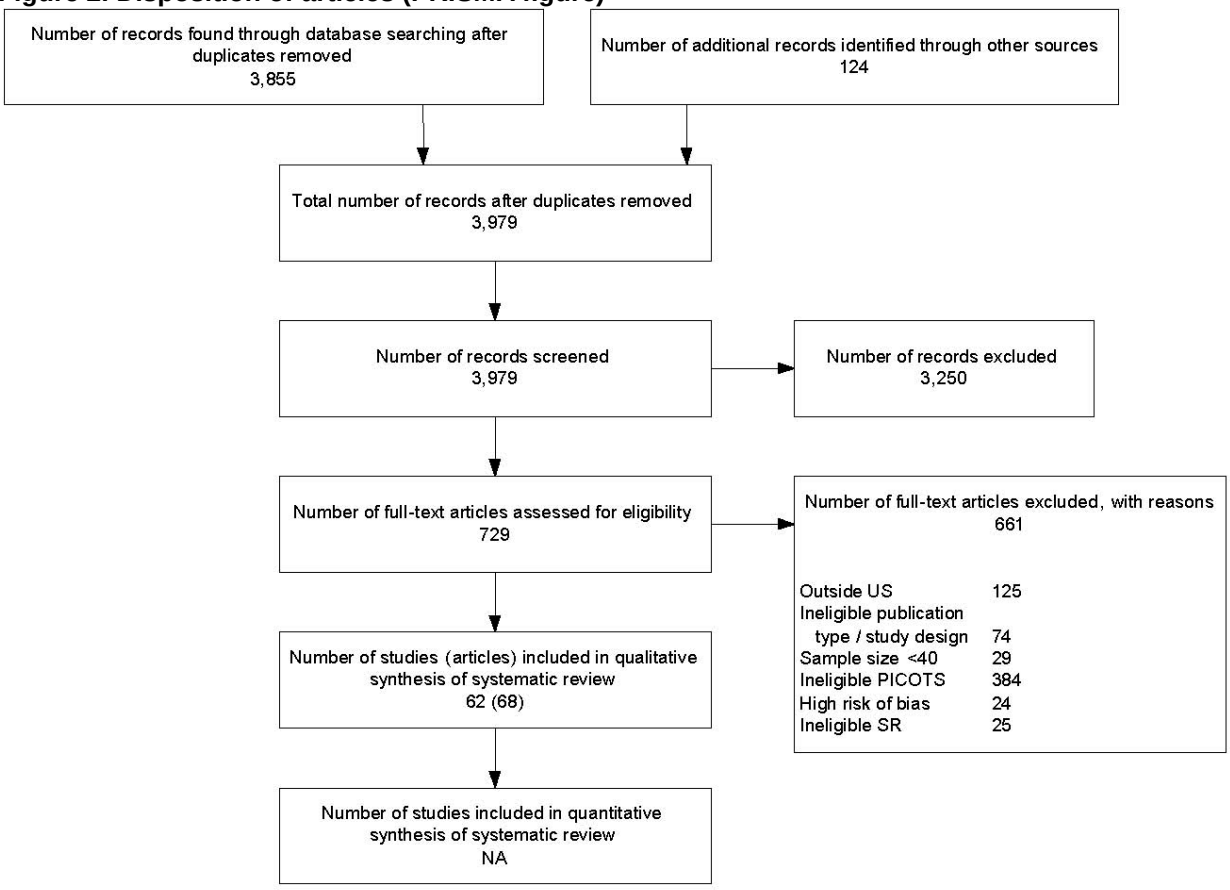
Figure 2 presents our literature search results. Literature searches through December 8, 2011, for the current report identified 3,855 unduplicated citations. Handsearches of systematic reviews and other sources added 124 citations. All these sources produced a total of 3,979 references. Appendix A provides a list of all search terms used and the results of each literature search.

After applying our eligibility and exclusion criteria to titles and abstracts of all identified citations, we obtained full-text copies of 729 published articles. We reapplied our inclusion criteria and excluded 637 of these articles from further review before risk of bias assessment; an additional 24 were rated as having high risk of bias. Appendix C provides a list of excluded studies and reasons for exclusion at the full-text stage.

Of the 92 articles included after full-text review, we dropped 24 articles from further analysis because of their high risk of bias. Thus, we included a total of 68 articles for qualitative synthesis. Evidence tables for these 68 articles are in Appendix D; risk of bias assessments for all 92 articles included after full-text review can be found in Appendix E.

The 68 articles included in this review represent 62 studies. Of the 68 included articles, 64 were randomized controlled trials (RCTs), and 4 were observational studies. Among the trials, 51 used a parallel randomization scheme, 12 used cluster randomization, and 1 used stratified randomization. Among the observational studies, 2 used a before–after design, 1 used an interrupted time series design with a concurrent control group, and 1 used a retrospective quasi-experimental design. We assessed 57 included articles as medium risk of bias and 11 as low risk of bias.

Figure 2. Disposition of articles (PRISMA figure)



Abbreviations: NA = not applicable; PICOTS = population, intervention, comparator, outcomes, timing, setting and study duration; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SR = systematic reviews; US = United States.

Key Question 1. Patient, Provider, and Systems Interventions

Descriptions of Included Studies

We found 57 studies (reported in 63 articles) that addressed patient, provider, systems, or combinations of these targets for medication adherence and other outcomes. As noted earlier, this KQ is organized by the clinical condition for which we found evidence: diabetes; hyperlipidemia; cardiovascular conditions, specifically hypertension, heart failure, and myocardial infarction; reactive airway disease, specifically asthma and chronic obstructive pulmonary disease (COPD); 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 any external taxonomy. The primary organizational principle for this KQ is clinical condition: using terminology specific to each clinical condition maintains and supports this organizational structure. 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, notes key points, and gives a detailed synthesis for each clinical condition in the order listed in Table 4. We support the analysis for each clinical condition with a summary table under key points showing overall findings. The detailed synthesis subsection for each clinical condition includes one table describing the characteristics of the trial and medication adherence outcomes for the clinical condition and separate strength-of-evidence tables for each intervention type. Entries in summary tables are presented by intervention type first, and then by the last name of the first author of the trial.

For each subsection on characteristics of the trial, we present an overview, followed by details on population, intervention, comparator, outcome and timing, and setting (i.e., PICOTS) and applicability. The key points distinguish "insufficient" grades for (a) bodies of evidence in which some research exists on the outcomes but is insufficient to make a call on the strength and (b) bodies of evidence in which no research exists.

As noted in the Introduction and Methods chapters, we synthesize evidence on other outcomes only for studies that had demonstrated a statistically significant difference in medication adherence outcomes or, occasionally, in outcomes related to either initiation or persistence of medication. As a result, strength-of-evidence grades of insufficient or low for any other outcomes reflect the paucity of the evidence on such outcomes, based on the subset of studies that demonstrate improvement in medication adherence. Strength-of-evidence grades for any other outcomes cannot be interpreted as evidence of effectiveness of intervention strategies that may alter health outcomes through mechanisms other than medication adherence. Appendix G includes summary tables for each health or other outcome.

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

Clinical Condition	Intervention	Comparator	Number of Studies
Diabetes	Case management/collaborative care	Usual care	3 Bogner et al., 2010[87] Grant et al., 2003[88] Lin et al., 2006[89]
Diabetes	Health coaching	Usual care	1 Wolever et al., 2010[90]
Diabetes	Education with social support	Education without social support	1 Pearce et al., 2005[91]
Hyperlipidemia	Collaborative care	Usual care	1 Lin et al., 2006[89]
Hyperlipidemia	Decision aids	Educational materials, no decision aid	2 Mann et al., 2010[92] Weymiller et al., 2007[93] Jones et al., 2009[94]
Hyperlipidemia	Education and behavioral support (phone or mail)	Usual care or less intense intervention	5 Guthrie et al., 2001[95] Johnson et al., 2006[96] Powell et al., 1995[97] Schectman et al., 1994[98] Stacy et al., 2009[99]
Hyperlipidemia	Multicomponent (education face-to-face with pharmacist + blister packaging)	Discontinuation of intervention	1 Lee et al., 2006[78]
Hypertension	Blister packaging	Usual care	1 Schneider et al., 2008[100]
Hypertension	Case management	Usual care	3 Bogner et al., 2007[101] Rudd et al., 2004[102] Wakefield et al., 2011[103]
Hypertension	Collaborative care	Usual care	3 Carter et al., 2009[104] Hunt et al., 2008[105] Lin et al., 2006[89]
Hypertension	Education and behavioral support (telephone, mail, and/or video)	Usual care	5 Bosworth et al., 2008[106,107] Bosworth et al., 2005[108] Friedman et al., 1996[109] Johnson et al., 2006[110] Powell et al., 1995[97]
Hypertension	Education (face-to-face with pharmacist)	Discontinuation of or less intense intervention	3 Lee et al., 2006[78] Solomon et al., 1998[111,112] Vivian et al., 2002[113]
Hypertension	Education with social support	Education without social support	1 Pearce et al., 2005[91]
Hypertension	Risk communication	Educational materials	1 Powers et al., 2011[114]
Heart failure	Reminder video and telephone calls	No reminder calls	1 Fulmer et al., 1999[115]
Heart failure	Multicomponent pharmacist-led	Usual care	1 Murray et al., 2007[116]
Heart failure	Case management	Usual care	1 Rich et al., 1996[117]
Heart failure	Access to medical records	Usual care (no access)	1 Ross et al., 2004[118]

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

Clinical Condition	Intervention	Comparator	Number of Studies
Myocardial infarction	Education and behavioral support	Usual care	1 Smith et al., 2008[119]
Reactive airway disease: Asthma	Self-management	Usual care	5 Bender et al., 2010[120] Berg et al., 1997[121] Janson et al., 2003[122] Janson et al., 2009[123] Schaffer et al., 2004[124]
Reactive airway disease: Asthma or COPD	Pharmacist or physician access to patient adherence information	Pharmacist training or usual care	2 Weinberger et al., 2002[125] Williams et al., 2010[126]
Reactive airway disease: Asthma	Shared or clinical decisionmaking	Clinical decisionmaking or usual care	1 Wilson et al., 2010[127]
Depression	Medication telemonitoring or telephone care	Usual care	2 Rickles et al., 2005[128] Simon et al., 2006[129]
Depression	Case management	Usual care	3 Bogner et al., 2007[101] Bogner et al., 2010[87] Katon et al., 2001;[130] Ludman et al., 2003;[131] Von Korff et al. 2003[132]
Depression	Collaborative care	Usual care	5 Capoccia et al., 2004[133] Katon et al., 1995[134] Katon et al., 1996[135] Katon et al., 1999;[136] Katon et al., 2002[137] Pyne et al., 2011[138]
Depression	Reminders to nonadherent patients and lists of nonadherent patients to providers	Usual care	1 Hoffman et al., 2003[139]
Glaucoma	Multicomponent intervention (educational video, discussion of barriers, reminder calls and dosing aid)	Usual care	1 Okeke et al. 2009[140]
Multiple sclerosis	Counseling (software-based telephone)	Less intense intervention	1 Berger et al., 2005[141]
Musculoskeletal diseases	Case management	Less intense intervention	1 Rudd et al. 2009[142]
Musculoskeletal diseases	Virtual osteoporosis clinic	Usual care	1 Waalen et al., 2009[143]
Musculoskeletal diseases	Decision aid	Usual care	1 Montori et al., 2011[144]
Multiple or unspecified chronic conditions	Outreach, education, and problem-solving (pharmacist-led)	Usual care	3 Nietert et al., 2009[145] Schnipper et al., 2006[146] Taylor et al., 2003[147]
Multiple or unspecified chronic conditions	Case management intervention	Usual care	1 Sledge et al., 2006[148]

Key Question 1. Diabetes: Medication Adherence Interventions

Description of Included Studies

Overview

We found five RCTs (five articles) that assessed the effects of five different interventions aimed at improving medication adherence among adult patients with diabetes mellitus.[87-91] Four trials had a medium risk of bias[88-91] and one trial[87] had a low risk of bias.

Population

Three trials reported limiting the sample to patients with type 2 diabetes or who were on oral hypoglycemic agents.[88,90,91] Two required a codiagnosis of depression[87,89] and one a codiagnosis of uncontrolled hypertension.[91]

Interventions

The interventions to improve adherence differed considerably, although all were directed at patients. Three trials additionally targeted the health system,[87-89] and one targeted providers.[88]

Two interventions used what the authors termed "integrative" approaches to disease management, each of which involved personalization of care:[87,90] integrative health coaching in one and the an integrated care model delivered by a care manager in the other. The former helped individuals to integrate their values with their own health behaviors and targeted only patients,[90] whereas in the latter, the care manager integrated the care the person was receiving—hence targeted both the patient and the system.[87] One trial focused on cardiovascular risk reduction provided education involving a social support person.[91]

In a pharmacist-delivered intervention,[88] pharmacists assessed patients' adherence barriers, provided tailored verbal patient education, and communicated these to physicians and social service providers. Finally, one trial attempted to improve adherence to diabetes treatment by individualizing depression management using collaborative care,[89] which required systems integration.

Taken together, these five intervention trials fell into three clusters of intervention types. One cluster involved a "case management/collaborative care" model, 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 care included enhancing communication between different provider types (e.g., between physicians and pharmacists[88] or between different subspecialists of physicians[89]) or using a care manager as a liaison between patient and physician.[87] Authors of the case manager trial pointed out that their intervention differed from other care manager trials by focusing on the care manager's role as a liaison between the patient and the physician[87] The trials in this cluster 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.

In the two other trials (one cluster each), one involved a "health coaching"[90] intervention and another implemented an intervention focused on education with a patient-designated "social support person."[91]

Comparator

Most trials compared an active arm with what was termed "standard of care" or "usual care." The content of such care was often not specified; when it was, it varied among trials. In the trial seeking to enhance diabetes adherence by improving depression management, usual care was treatment of depression by the primary care physician.[89] In the trial in which intervention participants received education via a social support person, the comparator was receipt of the same educational information without the involvement of a social support person.[91] 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.[88]

Outcome and Timing

Adherence to diabetes medications was defined and assessed in a wide variety of ways. Two of these five trials used a nonself-reported measure. The trial that used medication event monitoring system (MEMS) defined adherence as the percentage of participants taking more than 80 percent of their prescribed doses. The trial using pharmacy refill data defined adherence as the percentage of time that prescriptions were filled on time.

Among the three trials with only self-reported adherence, two used the Morisky Adherence Scale although each defined adherence differently.[90,91] One trial using a single item to ask about patients' medication taking, with a 7-day recall period,[88,90] defined adherence as the number of days that no doses were missed.[88]

Some trials evaluated effects on various intermediate outcomes (e.g., %HbA1C [glycosylated hemoglobin]) or ultimate health outcomes (e.g., health-related quality of life); we report on these below only when the impact on medication adherence was statistically significant.

Timing and frequency of the trials' assessments of outcomes assessments varied widely, ranging from 6 weeks to 12 months followup and from one to four times (every 3 to 6 months) Similarly, timing of the outcome assessment relative to administration or completion of the intervention differed across the trials.

Setting

Three trials were conducted in primary care settings.[87,89,91] One was performed in an outpatient tertiary care center clinic[90] and one in an academically affiliated community health center.[88]

Applicability

The diversity of settings in which these trials were conducted contributed to the overall applicability of the results. However, no trial assessed results among subgroups of patients with poorly controlled diabetes, limiting applicability of the results to that type of patient population.

Key Points

Overview

- All five RCTs assessed intervention effects on medication adherence (e.g., percentage of participants achieving a threshold of pills taken, proportion of pills taken), albeit each used a slightly different definition of medication adherence and tested different interventions (Table 5). One of the five trials (one of three testing a case

management/collaborative care model),[87] demonstrated a statistically significant effect of the intervention on medication adherence and a statistically and clinically important effect on hemoglobin percent A1c.

Table 5. Diabetes: summary of the evidence

Type of intervention	Studies, N Randomized	Adherence: Measure, Followup Period Overall Result (+/=/-) and Timing	Additional Outcomes: Outcome Overall Result (+/=/-) and Timing
Collaborative care/ case management	Bogner et al., 2010[87] N=58	+ Adherence (MEMS) for taking ≥80% oral hypoglycemic agents over 6 weeks	+ Percentage HbA1c (mean) at 6 weeks
	Grant et al., 2003[88] N=462	= Number of days in last 7 no doses were missed	NA
	Lin et al., 2006[89] N=329	= Percentage of days non-adherent (pharmacy refill data)	NA
Health coaching	Wolever et al., 2010[90]	= 4-item Morisky scale score at 6 months	NA
Education with social support	Pearce et al., 2005[91] N=199	= Morisky, proportion with high, medium, or low adherence at 2 months	NA

Abbreviations: (+) = statistically significant difference favoring intervention arm(s); (=) = no statistically significant difference; (-) = statistically significant difference favoring comparison arm; MEMS = medication event monitoring system; N = number; NA = not applicable

Case Management/Collaborative Care

- Medication adherence: One approach improved medication adherence among patients with diabetes, particularly those with comorbid depression (low strength of evidence).
- Biomarkers of clinical outcomes: The intervention that improvedadherence improved percent HbA1C—a difference of 1.2 percentage points between arms (low strength of evidence).

Health Coaching

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

Education With Social Support

- Medication adherence: One trial reported no significant differences between education with or without social support (insufficient).

Detailed Synthesis for Collaborative Care/Case Management Interventions for Diabetes

Medication Adherence

Of three trials testing the effects of coordinated care models on medication adherence,[87-89] one, assessed as low risk of bias, found a significant effect on adherence to both oral

hypoglycemic agents and antidepressants at 6 weeks followup.[87] The other two trials (both medium risk of bias) found no beneficial effect at 12[89] and 3 months,[88] respectively (Table 6).

The first of these three trials[87] assessed the effect of a case 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 trial showed large and statistically significant differences in adherence between intervention and control groups for both medications.

In the second such trial,[89] 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.[88]

Taken together, these trials provide low strength of evidence that coordinated care interventions improve medication adherence (Table 7).

Other Outcomes

HbA1C is sometimes considered a surrogate marker for adherence; however, because effects on HbA1c are considered to depend partly on adherence, we present this outcome only for the trial[87] that demonstrated a significant effect on adherence. It showed a statistically significant improvement in HbA1c among intervention group members at followup compared with controls (6.7% vs. 7.9%, p=0.019). This trial provides a low level of evidence that coordinated care interventions improve percent HgbA1c (Table 7).

Table 6. Diabetes: detailed medication adherence outcomes

Type of Intervention	Study N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, direction)	Source	Baseline	First Followup	Additional Followups
Case management/ collaborative care	Bogner et al., 2010[87] G1: 29 G2: 29	Adults ≥50 years with depression and diabetes Community primary care clinic	G1: Integrated care of depression and diabetes with care manager G2: Usual care	Three face-to-face + two calls over 4 weeks	Percentage of patients with ≥80% adherence to oral hypo-glycemics (0 to 100%)	MEMS	n (%) G1: 10 (34.5) G2: 6 (20.7) 95% CI, NR p:0.19	6 weeks: G1: 18 (62.1) G2: 7 (24.1) 95% CI, NR p:0.004	NR
	Grant et al., 2003[88] G1: 61 G2: 54 G3: 230	Adults with type 2 diabetes mellitus Academically affiliated community health center	G1: Pharmacist-administered questions, physician feedback, social service referrals G2: Pharmacist-administered questionnaire only G3: Set-aside lab controls	One phone session	Number of days in the last 7 that no doses were missed	Self-report	Mean number of days±SD G1: 6.7 ± 0.9 6.9 ± 0.4 P=0.3	3 months Mean change in number of days±SD G1: 0.1 (1) G2: 0.1 (0.4) 95% CI, NR p=0.8	NR
	Lin et al., 2006[89] G1: 164 G2: 165	Adults with diabetes mellitus and persistent depression Nine primary care clinics Washing-ton State	G1: Collaborative care for depression with medications or problem-solving G2: Advised to consult PCP for depression treatment	16 phone or face-to-face visits over 12 months	Percentage of days nonadherent to oral hypoglycemic (0-100%)	Pharmacy refill data	Mean % (SD) G1: 19.8 (21.3) G2: 22.9 (24.0) 95% CI, NR p: NS	12 months: Mean % (SD) G1: 28.2 (28.9) G2: 24.0 (24.7)	NR
					Adjusted mean difference in percentage of days nonadherent (baseline minus endpoint)	Pharmacy refill data	NR	12 months: –6.3 (–11.91 to –0.71) p=0.03	NR

Table 6. Diabetes: detailed medication adherence outcomes (continued)

Type of Intervention	Study N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, direction)	Source	Baseline	First Followup	Additional Followups
Education with social support	Pearce et al., G1: 50 G2: 58 G3: 91	Adults >21 years with type 2 diabetes mellitus and HTN 18 primary care practices Kentucky	G1: Nurse-delivered cardiovascular risk education with patient's social support person, quarterly educational newsletters G2: Same as G1 intervention G3: Same as G1 without social support person	One face-to-face session plus four quarterly news-letters	4-item Morisky Adherence Scale	Self-report	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	9 to 12 months Details NR, P NS	NR
Health coaching	Wolever et al., 2010[90] G1: 27 G2: 22	Adults with type 2 diabetes mellitus on oral hypo-glycemics Outpatient clinic at tertiary care center	G1: 6 months integrative health coaching G2: Usual care	14 phone sessions (either weekly, four biweekly; one monthly)	4-item Morisky Adherence Scale	Self-report	(Mean, SD) G1:6.7 (0.96) G2: 6.7 (1.25)	(Mean, SD): G1:7.2 (0.97) Within group change over time p=0.004 G2: 6.9 (1.25) Within group change over time p=NS 95% CI, NR p-value for between group differences in change: NS	NR

Table 6. Diabetes: detailed medication adherence outcomes (continued)

Type of Intervention	Study N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, direction)	Source	Baseline	First Followup	Additional Followups
Health coaching (continued)					One-item dichotomous question assessing whether patients missed dose in last 7 days	Self-report	G1:51.9 G2: NR	G1: 7.4 Within group change over time: p<0.001 G2: NR Within group change over time: NS 95% CI, NR p:for between group differences NR	NR

Abbreviations: CI = confidence interval; G = group; HbA1c = hemoglobin A1C; MEMS = medication event monitoring system; N = number; NR = not reported; NS = not significant; PCP = primary care physician; OR = odds ratio; SD = standard deviation.

Table 7. Case management/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
Collaborative care/case management 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 percentage points Low

Abbreviations: HbA1C = hemoglobin A1C; RCT = randomized controlled trial.

Detailed Synthesis for Health Coaching Intervention for Diabetes

Medication Adherence

One small trial, conducted at one site, assessed a program that included 14 telephone calls as a 6-month health coaching program. Health coaching was found to have no statistically significant effect at 12-month followup (Table 6).[90] Evidence is insufficient to determine whether health coaching interventions can improve medication adherence among patients with diabetes (Table 8).

Table 8. 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	Unknown	Direct	Imprecise	Difference between groups on 4-point scale: 0.3 Insufficient

Abbreviation: RCT = randomized controlled trial.

Detailed Synthesis for Social Support Intervention for Diabetes

Medication Adherence

One trial of education with social support 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 (Table 6).[91] Evidence is insufficient to determine whether including a social support person in a diabetes education effort improves medication adherence (Table 9).

Table 9. 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
Patient education with social support vs. patient education without social support	1; 199 (189)	Medication adherence	RCT Medium	Unknown	Direct	Imprecise	No significant difference between groups for Morisky scale scores at 12 months Insufficient

Abbreviation: RCT= randomized controlled trial.

Key Question 1. Hyperlipidemia: Medication Adherence Interventions

Description of Included Studies

Overview

Nine trials (10 articles) evaluated interventions to improve medication adherence among patients with hyperlipidemia.[78,89,92-99] We rated all nine trials as medium risk of bias.

Population

Three trials were conducted primarily among patients with elevated cholesterol,[96,98,99] one was among patients with both elevated risk of a first myocardial infarction and elevated cholesterol,[95] and two were among patients with diabetes;[92-94] three trials evaluated subgroups with hyperlipidemia.[78,89,97] All trials were conducted in adults 21 years and older[96,99] to 65 years or older.[78] In the seven trials that reported mean participant ages,[78,89,92-95,97,98] the range was from 54 to 55 years of age[97] to 78 years.[78] In the trials reporting proportion of female participants,[78,89,92-97,99] women made up between 22.9 percent[78] and 65 percent to 68 percent[97] of the trial populations. African-American participants were between 5.8 percent[96] and 32.3 percent[78] of the trial populations in the three trials that reported this information.[78,95,96]

Intervention

The nine trials evaluated diverse interventions, but all targeted patients; one trial additionally targeted systems of care.[98]

One trial evaluated the effect of collaborative care individualized to include either antidepressant medication or problem-solving treatment to promote adherence to medications, including angiotensin converting enzyme (ACE) inhibitors in a subgroup with hypertension.[89] Two trials tested a decision aid aimed at cardiovascular risk reduction choices to promote statin use.[92-94]

Five trials evaluated the effect of education and behavioral support on medication adherence.[95-99] In one trial the intervention included face-to-face education with a physician, 2 weeks of free pravastatin, telephone calls that served primarily as reminders, and educational mailings.[95] Another trial mailed an individualized, stage-matched intervention and manual for adherence to lipid-lowering medication based on the transtheoretical model for change.[96] A third

trial mailed one of four educational videotape programs to participants; these provided educational information on the patients' disease/condition process, medication(s), and the importance of adherence.[97] Another trial delivered an intervention through an initial face-to-face visit followed by telephone calls that addressed problems and adverse events associated with medications.[98] The final trial in this group delivered tailored behavioral support interventions via an interactive voice recognition (IVR) system supplemented by mailed printed materials.[99]

The final intervention for hyperlipidemia was a continuation of a multicomponent pharmacy-based intervention; it included visits with a clinical pharmacist to deliver individualized medication education and blister packaging of medications.[78]

Comparator

Active arms were compared with usual care in four of the nine trials.[89,96-98] Comparator arm activities varied among the intervention clusters. In the one trial of collaborative care, usual care consisted of advising participants to consult their primary care physician for treatment.[89] In the two trials evaluating statin decision aids, usual care patients received control educational printed materials.[92-94]

Among the five education and behavioral support interventions, the control group in one trial 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 made to the intervention group).[95] In two trials in this cluster, usual care consisted of not receiving mailed intervention materials.[96,97] In the fourth trial of education and behavioral support, usual care consisted of receiving no phone calls following an initial clinic visit.[98] In the fifth trial in this cluster, 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.[99]

In the multicomponent trial, after a 6-month phase in which both intervention and control groups received the intervention, the intervention was discontinued for the control group, which then received medications in pill bottles with a 90-day supply.[78]

Outcome and Timing

No trials reported on initiation of medication. Three trials reported on persistence of medication use; two trials used persistence measures from pharmacy refill or claims data[98,99] and the other used self-reported persistence measures at 3 months following the intervention.[93,94] Of the trials using pharmacy refill data to report persistence, one trial 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;[99] the other trial reported persistence as the proportion of participants refilling prescriptions for either niacin or a bile acid sequestrant (BAS) at 2 months.[98]

All nine trials reported medication adherence outcomes. Measures of adherence included pharmacy refill data in three trials,[89,97,99] pill counts in one trial,[78] and self-reported measures in five trials.[92-96,98] One trial used multiple measures: pharmacy refill data to report persistence and a self-reported measure to report adherence.[98] Three of four trials 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 trials[97,99] and by pill count

in one trial.[78] Self-reported adherence measures were ascertained through adherence-related questions in three trials[93-95,98] and a Morisky scale in one trial.[92] In addition, one trial ascertained self-reported adherence measures from both a stage of change algorithm and medication adherence scale scores.[96]

Of the four trials with either improved medication adherence or persistence outcomes,[78,93,94,96,99] three reported other outcomes. These additional outcomes included low-density-lipoprotein cholesterol (LDL-C) levels and changes in LDL-C levels from baseline to followup in one trial[78] and patient satisfaction in the two other trials.[92-94] The shortest trial lasted 3 months;[93,94] the longest lasted 18 months.[96] One trial reported adherence and persistence outcomes at 2 months, although the intervention was 6 months.[98] Two trials reported adherence at points during and at the conclusion of the intervention.[92,96] One trial reported adherence measured 3 months following the conclusion of the intervention.[93,94] The other five trials either reported adherence measured at the conclusion of the intervention[95] or reported average adherence or persistence measured throughout the intervention.[78,89,97,99] In the trial that reported LDL-C measures, outcomes were measured at the conclusion of the intervention (14 months); changes in LDL-C levels from 2 to 14 months were reported. This trial 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 RCT in which one group continued the intervention and one group discontinued the intervention.[78] Two trials that reported patient satisfaction measures obtained outcomes immediately following the intervention.[92-94]

Setting

Three trials were based in primary care clinics,[89,92,95] one of which involved participants enrolled in a pharmaceutical registry through their primary care clinic.[95] One trial was based in a metabolic specialty clinic.[93,94] Two trials were based in either a military medical center[78] or a Department of Veterans Affairs medical center (VAMC).[98] Two trials were conducted among either health maintenance organization (HMO) or preferred provider organization (PPO) members.[97,99] Finally, one trial 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.[96]

Applicability

Notable limitations to applicability included trials that were conducted only among select populations such as participants in a registry program who received a free 2-week supply of pravastatin,[95] HMO or PPO members in two trials,[97,99] patients cared for at a military medical center in one trial[78] and patients cared for at a VAMC in one trial.[98] After randomization, one trial additionally eliminated participants who expressed “no intention of picking up their prescription” for a statin within 7 days, were not aware of the prescription, or failed to answer at least 50 percent of the baseline assessment, which may have introduced selection bias.[99,p.243]

Key Points

Overview

- Medication adherence: Across nine trials, we found variable evidence for medication adherence or persistence. Four of nine trials found significant improvements in outcomes of either medication adherence or persistence (Table 10).

Table 10. Hyperlipidemia: summary of findings

Type of Intervention	Studies, N Randomized	Adherence: Measure, Followup Period Overall Result (+/=/-) and Timing	Additional Outcomes: Outcome Overall Result (+/=/-) and Timing
Collaborative care	Lin et al., 2006[89] N=329	= Percentage of days nonadherent to lipid-lowering medication over 12 months = Adjusted difference in percentage of days nonadherent comparing G1 and G2 over 12 months	NA
Decision aids	Mann et al., 2010[92] N=150	= Percentage with high adherence on Morisky scale at 3 and 6 months	NA
	Weymiller et al., 2007[93] Jones et al., 2009[94] N=98	+ Number missing no medication doses in prior week at 3 months = Percentage using statins at 3- month followup	Patient satisfaction items + Amount of information = Clarity of information + Helpfulness of information = Would recommend to others deciding on statins = Would prefer similar approach for other treatment choices + Overall acceptability
Education and behavioral support (phone or mail)	Guthrie et al., 2001[95] N=13,100	= Currently taking pravastatin as prescribed at 6 months = Proportion missing no doses of pravastatin in past 7 days at 6 months	NA
	Johnson et al., 2006[96] N=404	Among pre-action sample: + Stage of change algorithm: percentage reaching action or maintenance stage for adherence at 6 and 18 months + Medication adherence scale score at 6, 12, and 18 months = Adherence score on additional 5-item survey at 6 months + Adherence score on additional 5-item survey at 12 and 18 months Among post-action sample: = Percentage maintaining stage for adherence on 5-item survey at 6 and 12 months + Percentage maintaining stage for adherence on 5-item survey at 18 months	NR
	Powell et al., 1995[97] N=4246	= Medication possession ratio over 9 months, overall and for antihypertensive medications, over 9 months = Percentage of participants with ≥80% medication possession ratio, over 9 months, overall and for antihypertensive medications	NA
	Schectman et al., 1994[98] N=102 (Niacin) N=62 (Bile acid sequestrant)	= Number of medication doses missed in past week, at 2 months in both niacin and BAS groups = Proportion refilling prescription at 2 months in both niacin and BAS groups	NA

Table 10. Hyperlipidemia: summary of findings (continued)

Type of Intervention	Studies, N Randomized	Adherence: Measure, Followup Period Overall Result (+/=/-) and Timing	Additional Outcomes: Outcome Overall Result (+/=/-) and Timing
	Stacy et al., 2009[99] N=578	+ Medication possession ratio + ≥ 80% over 6 months + In possession of statin at the end of 6 months + Refilling statin within 30 days of the refill date over 6 months + Both MPR ≥ 80% and refilling statin within 30 days of refill date over 6 months	NR
Multicom-ponent (education face-to-face with pharmacist + blister packaging)	Lee et al., 2006[78] N=159	+ Proportion of pills taken over 6-month RCT + Percentage of participants with ≥ 80% adherence to medications over 6-month RCT	Among patients with hyperlipidemia: Biomarkers = LDL-C at 14 months (2-month run-in + 6-month cohort + 6-month RCT) = LDL-C difference between 2 months and 14 months (2-month run-in + 6-month cohort + 6-month RCT)

Abbreviations: (+) = statistically significant difference favoring intervention arm(s); (=) = no statistically significant difference; (-) = statistically significant difference favoring comparison arm; BAS = bile acid sequestrant; LDL-C = low density lipoprotein cholesterol; MPR = medication possession ratio; N = number; NA = not applicable; NR = not reported; RCT = randomized controlled trial.

- Other outcomes: Two of the four trials with either improved medication adherence or better persistence outcomes reported additional outcomes. One reported LDL-C, which was not different between groups; the other reported patient satisfaction outcomes for which some, but not all, outcomes were improved in the intervention group.

Collaborative Care Interventions for Hyperlipidemia

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

Decision Aids for Hyperlipidemia

- Medication adherence: One of two trials with improved medication adherence, overall small sample sizes and imprecise outcomes (insufficient evidence); persistence measured in one trial, no significant improvement (insufficient evidence).
- Patient satisfaction: Decision aid interventions improved patient satisfaction with some but not all aspects care (low strength of evidence of benefit).

Educational and Behavioral Support Interventions for Hyperlipidemia

- Medication adherence: Five trials with heterogeneous, and sometimes imprecise, outcomes reported some measures of improved medication adherence or persistence (low strength of evidence of benefit).

Multicomponent Intervention for Hyperlipidemia

- Medication adherence: One small trial reported improved medication adherence, but timing of measurement of the adherence outcome differed between groups (low strength of evidence of benefit).
- Biomarkers: Groups did not differ in LDL-C outcomes (insufficient evidence).

Detailed Synthesis for Collaborative Care for Hyperlipidemia

Medication Adherence

The trial of a collaborative care model resulting in individualized management of depression care did not identify a difference between groups for lipid-lowering agent adherence in subgroup analyses (Table 11).[89] Given the imprecise adherence outcomes and small sample size, the evidence was insufficient to draw any conclusions (Table 12).

Detailed Synthesis for Statin Decision Aids for Hyperlipidemia

Medication Adherence

Of the two trials of statin decision-aid interventions,[92-94] one found improved self-reported medication persistence in the intervention group compared with the control group, but only among participants on statins at 3 months following the intervention (Table 11).[93,94] The other trial of statin decision aids did not find improved adherence in the intervention group.[92] Because of small sample sizes and imprecise outcomes in medication adherence and persistence, we graded the evidence as insufficient (Table 13).

Other Outcomes

The one trial with improved adherence outcomes reported patient satisfaction outcomes (Appendix G).[93,94] This trial found higher odds of patient satisfaction for some but not all questions in the intervention group than in the control group. Scales ranged from 0 to 7 for all items with higher scores indicating better satisfaction; the odds of responding 6 or 7 out of 7 were calculated as an odds ratio comparing intervention to control group participants. Significant results were found for receiving an acceptable amount of information (OR, 3.4; 95% CI, 1.7 to 6.7), acceptable helpfulness of information (OR, 2.3; 95% CI, 1.4 to 3.8), and overall acceptability (OR, 2.8; 95% CI, 1.2 to 6.9). However, groups did not differ on items pertaining to clarity of information (OR, 1.6; 95% CI, 0.8 to 3.2), indicating that participants would recommend approach to others deciding on statins (OR, 2.6; 95% CI, 0.8 to 8.0), and indicating a preference for a similar approach for other treatment choices (OR, 1.5; 95% CI, 0.6 to 3.8). Because the evidence came from a small sample and some satisfaction outcomes were imprecise, we graded strength of evidence as low for benefit (Table 13).

Table 11. Hyperlipidemia: detailed medication adherence outcomes

Type of Intervention	Trial N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, direction)	Source	Baseline	First Followup	Additional Followups
Collab-orative care	Lin et al., 2006[89] Baseline: G1: 50 G2: 52 12 mos: G1: 54 G2: 63	Adults with diabetes mellitus and depression Primary care clinics	G1: Collaborative care for depression using either medications or problem-solving treatment G2: Advised to consult PCP for depression treatment	16 phone or face-to-face visits over 12 months	Percentage of days nonadherent to lipid-lowering agent (0-100%)	Pharmacy refill data	Baseline Mean (SD) G1: 29.3% (26.7%) G2: 24.5% (23.0%) 95% CI, NR p: NS	12 months: G1: 28.8% (27.1%) G2: 27.7% (24.0%) 95% CI, NR p: NS	NR
					Adjusted difference in percentage of days non-adherent to lipid-lowering agent comparing G1 and G2	Pharmacy refill data	NA	12 months: (%) = -0.2 95% CI: -7.23 to 6.76 p: NS	NR
Decision aids	Mann et al., 2010[92] G1: NR G2: NR	Adult patients with diabetes mellitus Urban primary care clinic	G1: Statin choice decision aid G2: ADA print material	One face-to-face session + printed material	Percentage with "good adherence" on 8-item Morisky Adherence Scale (0-100%)	Self-report	Baseline NR	3 months: Overall: 70% G1: NR G2: NR 95% CI, NR p: No significant difference between groups	6 months: Overall: 80% G1: NR G2: NR 95% CI, NR p: No significant difference between groups

Table 11. Hyperlipidemia: detailed medication adherence outcomes (continued)

Type of Intervention	Trial N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Decision aids (continued)	Weymiller et al., 2007[93] Jones et al., 2009[94] G1: 33 G2: 29 G1a: NR G1b: NR G2a: NR G2b: NR	Adults with Type 2 diabetes mellitus Metabolic specialty clinic	G1: Statin choice decision aid G1a: Research staff before visit G1b: Clinician during visit G2: Standard of care educational pamphlet control G2a: Research staff before visit G2b: Delivered by clinician during visit	One face-to-face session + printed material	Number missing no medication doses in the last week	Self-report	NR	3 months: G1: 31 G2: 23 OR: 3.4 95% CI: 1.5 to 7.5 p: NR	NR
					Number missing no medication doses in the last week, by mode of delivery	Self-report	NR	3 months: G1a: NR G1b: NR G2a: NR G2b: NR OR for delivery mode: 0.8 95% CI: 0.3, 2.6 p: NS	NR
	G1: 52 G2: 46				Percentage using statins at followup	Self-report	NR	3 months: N (%) G1: 33 (63%) G2: 29 (63%) 95% CI, NR p: NR OR: 1.4 95% CI: 0.8 to 2.4 p: NR	NR

Table 11. Hyperlipidemia: detailed medication adherence outcomes (continued)

Type of Intervention	Trial N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Education and behavioral support	Guthrie et al., 2001[95] G1: 3635 G2: 913	Adults with elevated MI risk and elevated cholesterol Primary care clinics	G1: Education from physicians, 2 weeks of free statin, two phone reminders, and four reminder postcards G2: Education from physicians, 2 weeks of free statin, no telephone calls, and two reminder postcards	Face-to-face + two phone calls + four mailings	Percentage reporting currently taking pravastatin as prescribed	Self-report	NR	6 months: G1: 79.7% G2: 77.4% 95% CI, NR p: NR	NR
					Percentage indicating that no doses missed in the past 7 days	Self-report	NR	6 months: G1: 64.3% G2: 61.8% 95% CI, NR p: NR	NR
	Johnson et al., 2006[96] G1: NR G2: NR	Adults 21 to 85 on cholesterol medication Multiple sources	G1: Mailed individualized computer-generated intervention and manual for lipid-lowering medication adherence. G2: Did not receive intervention materials	Three mailings over 6 months	Pre-action sample: percentage reaching action or maintenance stage for medication adherence; stage of change algorithm (0 to 100%)	Self-report	Baseline: G1: NR G2: NR 95% CI, NR p >0.05	6 months: G1: 55.3% G2: 40.0% OR: 1.80 95% CI, NR p<0.05	12 months: G1: NR G2: NR 95% CI, NR p=0.057 18 months: G1: 56.0% G2: 37.8% OR: NR 95% CI, NR p<0.01
					Pre-action sample: 4-item Medication Adherence Scale Score (better adherence with higher scores)	Self-report	Baseline: G1: NR G2: NR 95% CI, NR p >0.05	6 months: G1: NR G2: NR OR: 1.49 95% CI, NR p<0.01	12 months: G1: NR G2: NR OR: 1.62 95% CI, NR p<0.001 18 months: G1: NR G2: NR OR: 1.62 95% CI, NR p<0.01

Table 11. Hyperlipidemia: detailed medication adherence outcomes (continued)

Type of Intervention	Trial N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Education and behavioral support (continued)					Pre-action sample: Mean adherence score on 5-item survey (better adherence with lower scores)	Self-report	Baseline: G1: NR G2: NR 95% CI, NR p >0.05	6 months: G1: NR G2: NR OR: 2.03 95% CI, NR p>0.05	12 months: G1: NR G2: NR OR: 3.67 95% CI, NR p<0.01 18 months: G1: NR G2: NR OR: 2.86 95% CI, NR p<0.05
					Post-action sample: percentage maintaining action or maintenance stage for medication adherence; stage of change algorithm (0 to 100%)	Self-report	Baseline: G1: NR G2: NR 95% CI, NR p NR	6 months: G1: NR G2: NR OR: 2.12 95% CI, NR p>0.05	12 months: G1: NR G2: NR OR: NR 95% CI, NR p>0.05 18 months: G1: 85.0% G2: 55.6% OR: NR 95% CI, NR p<0.01

Table 11. Hyperlipidemia: detailed medication adherence outcomes (continued)

Type of Intervention	Trial N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Education and behavioral support (continued)	Powell et al., 1995[97] Overall G1: 1,993 G2: 2,253 Simva-statin G1: 271 G2: 297	Adults on benazepril, metoprolol, simvastatin or transdermal estrogen HMO members	G1: Mailed educational videotapes to improve adherence G2: Did not receive mailed videotapes	One mailed video	MPR (0 to 1)	Pharmacy refill data	NR	9 months: Overall Mean (SD) G1:0.70(0.23) G2:0.70(0.28) 95% CI, NR p: NR Simvastatin Mean (SD) G1:0.73(0.26) G2:0.70(0.28) 95% CI, NR p: NR	NR
					≥80% adherence by MPR ≥80% adherence by MPR	Pharmacy refill data	NR	9 months: Overall: N (%) G1:917 (46%) G2:998 (44%) 95% CI, NR p: NR Simvastatin G1:135 (50%) G2:138 (46%) 95% CI, NR p: NR	NR

Table 11. Hyperlipidemia: detailed medication adherence outcomes (continued)

Type of Intervention	Trial N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Education and behavioral support (continued)	Schectman et al., 1994[98] Niacin: G1: 40 G2: 40 BAS: G1: 18 G2: 22	Adults with hyperlipidemia on treatment with either niacin or bile acid sequestrant VA medical center	G1: Initial clinic visit + five calls for education and support G2: No telephone contact following initial clinic visit	One face-to-face + five calls over 28 days	"During the past week, how many doses of your medication have you missed?" (Proportion measured not described)	Self-report	NR	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	NR
					Percentage refilling prescription	Pharmacy refill data	NR	2 months: 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	NR

Table 11. Hyperlipidemia: detailed medication adherence outcomes (continued)

Type of Intervention	Trial N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Education and behavioral support (continued)	Stacy et al., 2009[99] G1: 253 G2: 244	Adults ≥21 years old with a new statin prescription HMO or PPO members	G1: Tailored behavioral support delivered via an IVR system + tailored printed mailed materials G2: Nontailored behavioral advice from a single IVR call + nontailored, printed materials	One to three IVR calls over 6 months	Percentage with MPR ≥80%	Pharmacy refill data	NR	6 months: G1: 47.0% G2: 38.9% Unadjusted OR: 1.39 90% CI: 1.03 to 1.88 Adjusted OR: 1.43 90% CI, 1.05 to 1.96 p: <0.10	NR
					Persistence: Percentage in possession of a statin at the end of 6 months	Pharmacy refill data	NR	6 months: 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	NR
					Continuous Persistence: statin prescription dispensed at least every 30 days after the refill date (no gaps >30 days)	Pharmacy refill data	NR	6 months: 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	NR

Table 11. Hyperlipidemia: detailed medication adherence outcomes (continued)

Type of Intervention	Trial N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Education and behavioral support (continued)					Both Continuous persistence (as defined above) and medication possession ratio ≥80%	Pharmacy refill data	NR	6 months: G1: 45.1% G2: 37.3% Unadjusted OR: 1.38 90% CI: 1.03 to1.86 Adjusted OR: 1.41 90% CI: 1.03 to 1.92 p: <0.10	NR
Multicom-ponent (education face-to-face, pharmacist + blister packaging)	Lee et al., 2006[78] G1: 83 G2: 76	Adults ≥65 taking ≥ four daily medications Pharmacy at U.S. military medical center	G1: Continuation of intervention: Face-to-face educational pharmacist visits and blister packing of medications G2: Discontinuation of intervention, medications provided in bottles	Seven face-to-face visits over 12 months	Percentage of pills taken vs. prescribed	Pill count	NR	6 months: Mean (SD) G1: 95.5% (7.7) G2: 69.1% (16.4) 95% CI, NR p<0.001	NR
	G1: 83 G2: 76				Percentage with ≥80% adherence	Pill count	NR	6 months: G1: 97.4% G2: 21.7% 95% CI, NR p<0.001	NR

Abbreviations: ADA = American Diabetes Association; BAS = bile acid sequestrant; CI = confidence interval; G = group; HMO = health maintenance organization; IVR = interactive voice recognition; MI = myocardial infarction; mos = months; MPR = medication possession ratio; N = number; NA = not applicable; NR = not reported; NS = not significant; OR = odds ratio; PCP = primary care provider; PPO = preferred provider organization; SD = standard deviation; U.S. = United States; VA = Department of Veterans Affairs

Table 12. Hyperlipidemia: strength of evidence for collaborative care intervention

Intervention	Number of Trials; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Hyperlipidemia: Collaborative care vs. usual care	1; 329 (117 on lipid-lowering meds)	Medication adherence	RCT Medium	Unknown	Direct	Imprecise	No sig diff between groups for percentage of days nonadherent (28.8% vs. 27.7%) or difference in change in adherence (-0.2%) over 12 months, pharmacy refill Insufficient

Abbreviations: diff = difference; RCT = randomized controlled trials; sig = significant; vs. = versus.

Table 13. Hyperlipidemia: strength of evidence for decision aid interventions

Intervention	Number of Trials; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Hyperlipidemia: Decision aids vs. educational materials with no decision aid	2; 248 (98 + NR in 1 trial)	Medication initiation, adherence, persistence	RCT Medium	Consistent	Direct	Imprecise	Variable self-report measures with variable outcomes Insufficient
	1; 98 (98)	Patient satisfaction	RCT Medium	Unknown	Direct	Imprecise	Variable self-report measures, some improvements for intervention group in specific areas Low

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

Detailed Synthesis for Education and Behavioral Support Interventions for Hyperlipidemia

Medication Adherence

Among the five trials that evaluated an intervention of education and behavioral support,[95-99] two trials reported improved adherence and/or persistence (Table 8).[96,99] To measure medication adherence or persistence, two trials used only self-reported survey items,[95,96] two trials used only pharmacy refill data,[97,99] and one used a combination of self-reported and pharmacy refill measures.[98]

In the two trials that found improved adherence or persistence measures, one found a higher percentage of participants in the intervention group with an MPR of 80 percent or more over 6 months than in the control group; however, this trial used a cutoff of $p<0.10$ (90% CI) for statistical significance.[99] This trial found better persistence as measured by the proportion in possession of a statin at the end of the 180-day intervention in the intervention group.[99] Other measures of persistence that were improved in the intervention group compared with the control group in this trial included the proportion of each group without a gap of more than 30 days in statin prescription refills and the proportion both without a gap of more than 30 days in statin prescription refills and MPR of 80 percent or more over months.[99] In other trial with adherence improvements, adherence was evaluated 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.[96] Among a "pre-action" portion of the trial sample, the proportion reaching Action or Maintenance was higher at 6 and 18 months, but not at 12 months, in the intervention group than in the control group. Among a "post-action" sample, the proportion maintaining Action or Maintenance was higher in the intervention group only at 18 months. 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.[96]

Among the three trials that did not find improved medication adherence or persistence outcomes, one found no difference between groups either for the number of patients who reported taking pravastatin as prescribed or for the percentage that reported missing no doses of pravastatin in the past 7 days at 6 months.[95] The second trial did not find improved adherence in MPR or proportion with an MPR of 80 percent or more between intervention and control groups over 9 months.[97] The third trial found no difference between groups either in self-report of missing medication doses in the past week or in the percentage refilling prescriptions. Given that only two of the five trials found improved persistence or adherence, the variability of measures, and imprecision in outcomes, evidence of improved adherence was graded as low for benefit (Table 14).

Table 14. Hyperlipidemia: strength of evidence for education and behavioral support interventions

Intervention	Number of Trials; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Hyperlipidemia: Education + behavioral support vs. usual care or less intense intervention	5; 18,492 (9,411 + NR in 1 trial)	Medication Adherence, persistence	RCT, medium	Consistent	Direct	Imprecise	Variable measures (self-report, pharmacy refill) with variable outcomes Low

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

Detailed Synthesis for Multicomponent Intervention for Hyperlipidemia

Medication Adherence

The one pharmacist intervention found improved medication adherence outcomes in the intervention group compared with the control group (Table 8).[78] This trial evaluated adherence from pill counts both as the percentage of 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).[78] However, pill counts were performed less frequently in the control arm (once over 6 months) than the intervention arm (three times over 6 months). Because adherence outcomes were at risk of bias in this relatively small trial, we graded strength of evidence as insufficient (Table 15).

Other Outcomes

This small trial 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). We graded the strength of evidence for no differences in this biomarker as insufficient. (Table 15).

Table 15. Hyperlipidemia: strength of evidence for multicomponent intervention

Intervention	Number of Trials; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Hyperlipidemia: Multicompo-nent (face-to-face education with a pharmacist and blister packaging) vs. discontinuation of intervention	1; 159 (159)	Medication adherence	RCT Medium	Unknown	Indirect	Precise	Improved in intervention group over 6 months, outcome at risk of bias due to differing measurement frequency: (1) Percentage adherence (95.5% vs. 69.1%) (2) Percentage with ≥80% adherence (97.4 vs. 21.7) Insufficient
	1; 159 (135)	Biomarkers LDL-C	RCT Medium	Unknown	Indirect	Imprecise	No difference between groups Insufficient

Abbreviations: LDL-C = low density lipoprotein cholesterol; RCT = randomized controlled trial.

Key Question 1. Hypertension: Medication Adherence Interventions

Description of Included Studies

Overview

Seventeen RCTs (19 articles) evaluated interventions to improve medication adherence in patients taking medications for hypertension.[78,89,91,97,100-114] Ten trials primarily evaluated patients with a hypertension diagnosis,[100,102,104-110,113,114] one evaluated patients with hypertension and depression,[101] two evaluated patients with diabetes mellitus and hypertension,[91,103] and four evaluated subgroups with hypertension.[78,89,97,111,112] We rated 16 trials as having medium risk of bias[78,89,91,97,101-114] and one trial as having low risk of bias.[100]

Population

All trials were conducted in adults ranging from 18 years or older[110] to 65 years or older;[78,100] mean ages ranged from 54 to 55 years[97] to 78 years.[78] Women made up between 0 percent[113] and 75 percent[101] of the trial populations. Among the two trials that reported race and ethnicity, the proportion of Black participants ranged from between 8 percent to 11 percent[102] up to 70 percent to nearly 85 percent.[113]

Intervention

All 17 trials evaluated interventions that were targeted at patients. Five trials additionally targeted systems of care,[101,102,104,105,113] and one trial additionally targeted providers.[104]

One trial evaluated the effect of blister packaging medications.[100]

Three trials evaluated the effect of case management (two involving nurses).[101-103] In one trial an integrated care manager delivered the intervention both in person and by telephone for patients with depression and hypertension.[101] In another, a nurse managed hypertension medications by telephone as guided by home blood pressure readings.[102] In the third trial, a nurse managed blood pressure and glucose data that was collected by a home telehealth device and determined whether further education or other management changes were needed.[103]

Three trials evaluated collaborative care models.[89,104,105] Two collaborative care trials evaluated a primary care physician/pharmacist collaboration for hypertension care.[104,105] The third evaluated the effect of collaborative care for depression with individualized management using either antidepressant medication or problem-solving treatment to promote adherence to medications, including angiotensin-converting enzyme (ACE) inhibitors in a subgroup with hypertension.[89]

Five trials examined interventions that provided education and behavioral support by either telephone or mail.[97,106-110] In two trials, a nurse delivered education and support by telephone.[106-108] In a third, an interactive computer-based telecommunications system delivered the education and support by telephone.[109] The remaining two trials delivered interventions by mail;[97,110] one evaluated the effect of mailing an individualized intervention and manual for antihypertensive adherence based on the transtheoretical model for change[110] and the other evaluated the effect of mailing educational videotape programs about the participants' medications and inferred diseases.[97]

Of the remaining trials, three evaluated interventions that involved between five[111,112] and seven[78] face-to-face educational visits with a pharmacist.[78,111-113] In two of these interventions pharmacists delivered education and counseling about adherence;[78,111,112] in the third trial, pharmacists additionally managed participants' hypertension medications.[113]

Finally, one trial evaluated the effect of education and social support by involving a patient's social support person in an educational session delivered face-to-face by a nurse.[91] Another trial evaluated the effect of personalized risk communication for coronary heart disease and stroke.[114]

Comparator

Twelve trials compared active arms to usual care;[89,97,100-103,105-110,113] the remaining trials involved more than simple usual practices.[78,91,104,111,112,114] In the blister packaging intervention, the control group received medications in pill bottles instead of the blister packs provided to the intervention group.[100] In the trials of case management, usual care included typical clinical care in one trial[101,103] and was minimally described in the other trial.[102]

Among the three trials of collaborative care, usual care involved the typical clinical care offered to patients in two trials;[89,105] in the third trial, control participants did not have contact with pharmacists but did have contact with trial nurses, who measured blood pressures and provided education.[104]

Among the education and behavioral support interventions, usual care consisted of no telephone contact with the control group in two trials,[106-108] no mailings to the control group in one trial,[97] and was minimally described in two trials.[109,110] In one of the three trials of face-to-face education with a pharmacist, the investigators discontinued the intervention after a 6-month phase in which both intervention and control groups received pharmacist visits and blister packages of medications.[78] In another trial of face-to-face education, the control group had two visits with a pharmacist, one at baseline and one between 4 and 6 months, with no supplemental

services or visits.[111,112] In the third trial of face-to-face education, the control group received typical clinical care with no pharmacist visits.[113]

In the trial evaluating education and social support, a social support person was not included in the nurse-delivered educational session for the control group.[91] In the risk communication trial, the control group received nonpersonalized educational information about heart attack and stroke risk.[114]

Outcomes and Timing

Medication adherence measures varied widely. None of the trials evaluated initiation of medication therapy; two evaluated persistence of medication therapy.[100,113] Self-reported adherence measures included nonvalidated survey measures in two trials,[110,113] a stage-of-change algorithm in one trial,[110] and Morisky scales in eight trials.[91,103-108,111,112,114] Additional adherence measures included pill counts in two trials,[78,109] pharmacy refill data in four trials,[89,97,100,113] and the MEMS in two trials.[101,102] One trial used both self-reported (survey questions) and nonself-reported (pharmacy refill data) measures of adherence.[113]

Of the five trials for which we discuss blood pressure outcomes, three reported systolic and diastolic blood pressure measurements (mm Hg) at followup;[78,101,111,112] two reported mean changes (mm Hg) in systolic and diastolic blood pressure between baseline and followup,[102,109] and one reported the proportion of patients with reductions in systolic and diastolic blood pressure between baseline and followup.[100]

Other outcomes included the occurrence of angina, myocardial infarction, and stroke (one trial).[100] Two trials reported on health care utilization, including emergency department (ED) visits and hospitalizations;[100,111,112] one additionally reported number of contacts with health care providers other than pharmacists.[111,112] Patient satisfaction and quality-of-life outcomes were reported in one trial from an unvalidated survey question.[111,112]

The length of these trials varied considerably; the shortest lasted 6 weeks[101] and the longest were planned to last 24 months,[106-108] although the publications we identified for both 24-month trials reported only 6-month outcomes.

In most trials, adherence outcomes were collected at the conclusion of the intervention. Exceptions include the 24-month trials reporting only 6-month outcomes,[106-108] one trial of an 18-month intervention that reported 6-, 12-, and 18-month outcomes,[110] and a 12-month trial that reported 6- and 12-month outcomes.[100] One trial lasted 14 months; it had an initial 2-month run-in period followed by a 6-month cohort intervention followed by a final 6-month RCT in which one group continued the prior cohort intervention and one group did not.[78]

Setting

Eleven trials focused on primary care populations,[89,91,100-108,114] three on pharmacy populations,[78,111-113] two on HMO populations,[97,110] and one recruited participants from community sites including senior centers.[109] Of the 17 trials, 5 were conducted within a population at least partly composed of patients from Veterans Administration medical centers (VAMCs),[103,108,111-114] and one was in a U.S. military medical center.[78]

Applicability

Overall, the six trials that were based within VAMCs and the military hospital were considered to have relatively limited applicability (except perhaps to those relevant populations).[78,103,107,108,111-114] Compared with the trials in other settings, the VA and military

populations studied included a lower proportion of women (ranging from 0 to 22 percent) and, with the exception of one trial conducted in an Iowa VA primary care clinic,[103] a higher proportion of Black participants (ranging from 32.3 percent to 80 percent to nearly 85 percent). In addition, one trial performed at a VAMC was considered to have limited generalizability because a large component of the intervention involved having a pharmacist prescribe medications,[113] which is a role available to pharmacists only within the VA system and a small number of states.

The two trials that were based in HMO populations tended to have a younger mean age (54 to 55.7 years old) than trials conducted in other populations.[97,110]

Key Points

Overview

- Medication adherence: Across 17 trials, evidence for medication adherence varied substantially (Table 16). Seven of the 17 trials reported significant improvements in at least one measure of medication adherence. The other 10 trials demonstrated no difference between groups for adherence to antihypertensive medications.
- Morbidity: Six of the seven trials with improved medication adherence reported blood pressure outcomes. Four of the six trials reported improvements in systolic blood pressure; four of the six reported improvements in diastolic blood pressure.
- We graded strength of evidence formally for five intervention clusters: (1) blister packaging of medications, (2) case management, (3) collaborative care, (4) education and behavioral support (telephone, mailing, or videotape), and (5) education (face-to-face with pharmacist). We graded the body of evidence for education with social support and for risk communication as insufficient.

Table 16. Hypertension: summary of findings

Type of Intervention	Studies, N Randomized	Adherence: Measure, Followup Period Overall Result (+/=/-) and Timing	Additional Outcomes: Outcome Overall Result (+/=/-) and Timing
Blister packaging	Schneider et al., 2008[100] N=93	+ Percentage of patients refilling medications on time over 12 months + Medication possession ratio over 12 months	Morbidity = Systolic blood pressure change at 6 months and 12 months = Diastolic blood pressure change at 6 and 12 months = Proportion of patients with reduced systolic blood pressure at 6 and 12 months = Proportion of patients with reduced diastolic blood pressure at 6 months + Proportion of patients with reduced diastolic blood pressure at 12 months = Occurrence of angina at 6 and 12 months = Occurrence of MI at 6 and 12 months = Occurrence of stroke at 6 and 12 months Health care utilization = ED visits and hospitalizations at 6 and 12 months
Case management	Bogner et al., 2007[101] N=64	+ Adherence for taking ≥80% hypertensive medications over 6 weeks	Morbidity + Systolic blood pressure (mean) at 6 weeks + Diastolic blood pressure (mean) at 6 weeks
	Rudd et al., 2004[102] N=150	+ Adherence for number of days medications taken correctly over 6 months	Morbidity + Systolic blood pressure (change), from baseline to 6 months + Diastolic blood pressure (change), from baseline to 6 months
	Wakefield et al., 2011[103] N=302	= Morisky scale scores at 6 months	NA
Collaborative care	Carter et al., 2009[104] N=402	= Morisky scale, percentage of patients reporting low medication adherence at 6 months = Morisky scale, within-group change in percentage of patients reporting low adherence from baseline to 6 months	NA
	Hunt et al., 2008[105] N=463	= Morisky scale, percentage of patients reporting high medication adherence at 12 months = Morisky scale, change in report of high medication adherence, from baseline to 12 months	NA

Table 16. Hypertension: summary of findings (continued)

Type of Intervention	Studies, N Randomized	Adherence: Measure, Followup Period Overall Result (+/=/-) and Timing	Additional Outcomes: Outcome Overall Result (+/=/-) and Timing
	Lin et al., 2006[89] N=329	= Percentage of days nonadherent to hypertension medication over 12 months = Adjusted difference in percentage of days nonadherent comparing G1 and G2 over 12 months	NA
Education and behavioral support (telephone, mail, and/or video)	Bosworth et al., 2008[106,107] N=636	= Morisky scale, percentage reporting high adherence at 6 months = Morisky scale, change in percentage reporting adherence from baseline to 6 months	NA
	Bosworth et al., 2005[108] N=588	= Morisky scale, change in proportion reporting adherence from baseline to 6 months	NA
	Friedman et al., 1996[109] N=299	= Unadjusted adherence to hypertensive medication by pill count, change from baseline to 6 months + Adjusted adherence to hypertensive medication by pill count, change from baseline to 6 months	Morbidity = Systolic blood pressure change from baseline to 6 months = Diastolic blood pressure change from baseline to 6 months
	Johnson et al., 2006[110] N=1227	= Behavioral measure of nonadherence at 6 months + Behavioral measure of nonadherence at 12 months and 18 months	NR
	Powell et al., 1995[97] N=4246	= Medication possession ratio over 9 months, overall and for antihypertensive medications, over 9 months = Percentage of participants with ≥80% medication possession ratio, over 9 months, overall and for antihypertensive medications	NA
Education (face-to-face with pharmacist)	Lee et al., 2006[78] N=159	+ Proportion of pills taken over 6-month RCT + Percentage of participants with ≥80% adherence to medications over 6-month RCT	Among patients with hypertension: Morbidity + Systolic blood pressure (mean) at 14 months (2-month run-in + 6-month cohort + 6-month RCT) + Systolic blood pressure difference between 2 months and 14 months (2-month run-in + 6-month cohort + 6-month RCT outcome) = Diastolic blood pressure at 14 months (6-month cohort + 6-month RCT outcome) =

Table 16. Hypertension: summary of findings (continued)

Type of Intervention	Studies, N Randomized	Adherence: Measure, Followup Period Overall Result (+/=/-) and Timing	Additional Outcomes: Outcome Overall Result (+/=/-) and Timing
Education (face-to-face with pharmacist) (continued)	Lee et al., 2006[78] N=159 (continued)		= Diastolic blood pressure difference between 2 months and 14 months (2-month run-in + 6-month cohort + 6-month RCT outcome)
	Solomon et al., 1998[111,112] N=133 (Hypertension)	Among patients with hypertension: + Morisky scale score, reporting compliance at 4- to 6-month visit + Morisky scale score, difference in proportion reporting compliance between baseline and 4- to 6-month visit; improved in G1 not G2	Among patients with hypertension: Morbidity + Systolic blood pressure (mean) at 4- to 6-month visit + Systolic blood pressure difference from baseline to 4- to 6-month visit within intervention group = Diastolic blood pressure (mean) at 4 to 6 months = Diastolic blood pressure difference from baseline to 4- to 6-month visit within intervention group Quality of life = Sexual dysfunction, dizziness and headaches at 4 to 6 months Patient satisfaction + Four medication-related questions at 4 to 6 months = One medication-related question at 4 to 6 months Health care utilization = Emergency department visits over 4 weeks prior, at 4 to 6 months + Hospitalizations over 4 weeks prior, at 4 to 6 months (one-tailed p<0.05) + Contacts with other health care providers (MD, NP, PA or RN) over 4 weeks prior, at 4 to 6 months (one-tailed p<0.05)
	Vivian et al., 2002[113] N=56	= Compliance survey questions at 6 months = Proportion of patients that received refills within 2 weeks of next scheduled refill date over 6 months	NA
Education with social support	Pearce et al., 2005[91] N=199	= Morisky, proportion with high, medium, or low adherence at 12 months	NA
Risk communica-tion	Powers et al., 2011[114] N=89	= Morisky, proportion with high adherence at 3 months	NA

Abbreviations: (+) = statistically significant difference favoring intervention arm(s); (=) = no statistically significant difference; (-) = statistically significant difference favoring comparison arm; ED = emergency department; G = group; MD = physician; MI = myocardial infarction; N = number; NA = not applicable; NP = nurse practitioner; NR = not reported; PA = physician assistant; RCT = randomized controlled trial; RN = registered nurse.

Key Points by Intervention Type

Blister Packaging of Medications

- Medication adherence: The trial that evaluated blister packaging of medication without additional intervention components reported significantly improved medication adherence and persistence (low strength of evidence of benefit).
- Morbidity: The blister packaging trial did not show a difference between groups for change in systolic or diastolic blood pressure at either 6 or 12 months. It did not show a significant difference between groups in the proportion of patients with reduced systolic blood pressure at 6 or 12 months or in the proportion with reduced diastolic blood pressure at 6 months. However, significantly more patients in the intervention than in the control group had reduced diastolic blood pressure at 12 months. These outcomes are all graded insufficient evidence for either no difference or benefit. This trial found no difference between groups for occurrence of angina, myocardial infarction, or stroke (insufficient evidence).
- Health care use: This trial demonstrated no significant difference between groups for ED visits and hospitalizations (insufficient evidence).

Case Management

- Medication adherence: Two of three trials that involved case management reported significantly improved medication adherence (low strength of evidence of benefit).
- Morbidity: These two trials reported blood pressure outcomes. One trial found significantly reduced mean systolic and diastolic blood pressures in the intervention group compared with the control group at 6 weeks; the other trial found systolic and diastolic blood pressure at 6 months were decreased more in the intervention than in the control group (low strength of evidence of benefit).

Collaborative Care

- Medication adherence: Among three trials evaluating collaborative care, none found improved medication adherence (low strength of evidence of no benefit).

Education and Behavioral Support

- Medication adherence: Among the five trials that evaluated education and behavioral support, two found significantly improved medication adherence; however, the trials used variable measures to assess medication adherence and some outcomes were imprecise (low strength of evidence of benefit).
- Morbidity: In one of the two trials with improved medication adherence, systolic and diastolic blood pressures did not differ between groups at 6 months (insufficient evidence).

Education (Face-to-Face With Pharmacist)

- Medication adherence: Among the three trials that evaluated education delivered face-to-face by a pharmacist, two found improved medication adherence; however, the trials used variable measures to assess medication adherence and had some imprecise outcomes (low strength of evidence of benefit). One trial evaluated medication persistence and found no difference between groups (insufficient evidence).

- Morbidity: Both trials with improved medication adherence found improvements in mean systolic blood pressure in the intervention arm compared with the control arm (moderate strength of evidence of benefit). No significant differences in mean diastolic blood pressure were identified between groups in either trial (insufficient).
- Quality of life: One trial reported quality-of-life outcomes, which did not differ between groups for sexual dysfunction, dizziness, or headaches (insufficient evidence).
- Patient satisfaction: One trial reported patient satisfaction outcomes from survey questions related to medications. The intervention group had better satisfaction scores than the control group for four of five questions (low strength of evidence of benefit).
- Health care utilization: One trial found no difference between groups for ED visits (insufficient evidence). Hospitalizations and contacts with various health care providers (physicians, nurses and nurse practitioners, physician assistants) were significantly lower in the intervention group than the control group (low strength of evidence of benefit).

Education With Social Support

- Medication adherence: The one trial that evaluated education with social support reported no difference in medication adherence between groups (insufficient evidence).

Risk Communication

- Medication adherence: The one trial that evaluated risk communication reported no difference in medication adherence between groups (insufficient evidence).

Detailed Synthesis for Blister Packaging of Medications for Hypertension

Medication Adherence

The intervention of blister packaging of medications improved both adherence and persistence in the intervention compared with the control group (using pharmacy refill data) (Table 17).[100] This trial found both a significantly higher percentage of patients who had prescriptions refilled on time and a higher MPR (medications received: medications prescribed) over 12 months in the intervention arm (Table 18). We graded the strength of evidence of benefit for persistence and adherence as low.

Other Outcomes

This trial reported one significant finding:[100] the proportion of patients with reduced diastolic blood pressure at 12 months was higher in the intervention than the control group (48.0% vs. 18.2%, p=0.031 (insufficient evidence of benefit) (Table 18). It found no significant differences for absolute systolic or diastolic blood pressures at 6 or 12 months, proportion of patients with reduced systolic blood pressure at 6 or 12 months, or proportion with reduced diastolic blood pressure at 6 months (all insufficient evidence). It reported the occurrence of angina, myocardial infarction, and stroke, none of which differed between the groups (insufficient evidence); it found no difference in ED visits and hospitalizations between at 6 and 12 months (insufficient evidence).

Table 17. Hypertension: detailed medication adherence outcomes

Study	N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Blister packaging	Schneider et al., 2008[100] G1: 47 G2: 38	Adults >65 with HTN Primary care clinic	G1: Blister packaging of lisinopril G2: No blister packaging of lisinopril	Monthly blister packs for 12 months	Percentage refilling medications on time (+/- 5 days of refill date) (0 to 100%)	Pharmacy refill data	NR	12 months: Mean (SD) G1: 80.4% (21.2) G2: 66.1% (28.0) 95% CI, NR p: 0.012	NR
					Medication possession ratio (0 to 100%)	Pharmacy refill data	NR	12 months: Mean (SD) G1: 0.93 (11.4) G2: 0.87 (14.2) 95% CI, p: 0.039	NR
Case manage-ment	Bogner et al. 2007[101] G1: 32 G2: 32	Adults ≥50 with depression and HTN Primary care clinic	G1: Integrated care of depression and hypertension with care manager G2: Usual care	Three face-to-face + two calls over 4 weeks	Number of patients with ≥80% adherence to hypertension medications (0 to 100%)	MEMS	NR	6 weeks: G1: 25 (78.1%) G2: 10 (31.3%) p<0.001 95% CI, NR	NR
	Rudd et al., 2004[102] G1: NR G2: NR	Adults with HTN Primary care clinic	G1: Nurse management by phone, HTN medication adjustment guided by home BPs G2: Not described	Five calls over 4 months	Adherence to daily medications (0 to 100%)	MEMS	NR	6 months: Mean (SD) G1: 80.5% (23.0) G2: 69.2% (31.1) 95% CI, NR p=0.03	NR
	Wakefield et al., 2011[103] G1: NR G2: NR G3: NR	Adults with diabetes mellitus and HTN Primary care clinic at VA medical center	G1: High-intensity: use of home telehealth device for blood pressure and glucose as well as education with nurse case management. G2: Low –intensity: Similar to G1 intervention with lower intensity of educational content. G3: Usual care	6 months, daily entries for BP and glucose	Morisky scale	Self-report	NR	6 months: G1: NR G2: NR G3: NR p: Per text no significant difference between groups; all groups improved from baseline; NR if statistically significant	NR

Table 17. Hypertension: detailed medication adherence outcomes (continued)

Study	N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Collab-orative care	Carter et al., 2009[104] G1: 192 G2: 210	Adults >21 with HTN Family medicine residency programs	G1: Collaborative model between pharmacists and physicians G2: No collaboration with pharmacists	Baseline visit+ telephone calls over 6 months	Percentage with low adherence on Morisky scale (0 to 100%)	Self-report	Baseline Mean (SD) G1:17.3% (27.5) G2: 18.7% (22.0) 95% CI, NR	6 months: Mean (SD) G1: 14.6% (25.4) G2: 14.7% (20.9) 95% CI, NR Within-group change from baseline to 6 months: G1: -2.7% p=0.979 G2: -4% p=0.602	NR
	Hunt et al., 2008[105] G1: 142 G2: 130	Adults with HTN Primary care clinics	G1: Collaborative primary care-pharmacist HTN management. G2: Usual care	Between one to four face-to-face visits over 12 months	Percentage with high adherence on Morisky scale (0 to 100%)	Self-report	Baseline G1: 61% G2: NR	12 months: G1: 67% G2: 69% 95% CI, NR p: 0.771 Within-group change from baseline to 12 months: G1: +6% p=0.08 G2: NR p NR	NR
	Lin et al., 2006[89] Baseline: G1: 54 G2: 65 12 mos: G1: 59 G2: 52	Adults with diabetes mellitus and depression Primary care clinics	G1: Collaborative care for depression using either medications or problem-solving treatment G2: Advised to consult PCP for depression treatment	16 phone or face-to-face visits over 12 months	Percentage of days nonadherent to ACE inhibitor (0 to 100%) Adjusted difference in	Pharmacy refill data Pharmacy refill data	Baseline Mean (SD) G1: 27.4% (27.1) G2: 29.7% (29.3) 95% CI, NR p: NS	12 months: Mean (SD) G1: 24.2% (22.7%) G2: 18.9% (17.4%) 95% CI, NR p: NS 12 months: (%)=-2.5% 95% CI, -8.69 to 3.70 p: NS	NR

Table 17. Hypertension: detailed medication adherence outcomes (continued)

Study	N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Collab-orative care (continued)	Baseline: G1: 54 G2: 65 12 mos: G1: 59 G2: 52				percentage of days nonadherent to ACE inhibitor comparing G1 and G2				
Education and behavioral support	Bosworth et al., 2008[106,107] G1: 319 G2: 317	Adults with HTN Primary care clinics	G1: Nurse delivered behavioral and educational intervention by phone G2: No telephone contact, usual care	12 calls every 2 months over 24 months planned	Percentage with high adherence on Morisky scale (0 to 100%)	Self-report	Baseline G1: 63% G2: 67% 95% CI, NR p: NR	6 months: G1: 72% G2: 68% 95% CI, NR p: NR Within-group change from baseline to 6 months: G1: + 9% G2: + 1% 95% CI, NR p: NR	NR
	Bosworth et al., 2005[108] G1: NR G2: NR	Adults with HTN Primary care clinics at VA medical center	G1: Nurse delivered behavioral and educational intervention by phone G2: No nurse telephone contact, usual care	12 calls every 2 months over 24 months planned	Difference in change of percentage with high adherence on Morisky scale (0 to 100%)	Self-report	NR	Change from baseline to 6 months: 0.74% 95% CI: -6.2 to 7.6 p: NR	NR
	Friedman et al., 1996[109] G1: 133 G2: 134	Adults $\geq$ 60 on medication for HTN Community-based	G1: An interactive computer-based telecommunications system (TLC) that conversed with patients in homes G2: Regular medical care (not described)	24 TLC calls over 6 months	Change in percentage of pills taken vs. prescribed	Pill count	NR	Change from baseline to 6 months: Unadjusted: G1: +2.4% G2: +0.4% p=0.29 Adjusted: G1: +17.7% G2: +11.7% p=0.03	NR

Table 17. Hypertension: detailed medication adherence outcomes (continued)

Study	N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Education and behavioral support (continued)	Johnson et al., 2006[110] G1: NR G2: NR	Adults 18-80 on medication for HTN HMO members	G1: Mailed individualized computer-generated intervention and manual for HTN medication adherence. G2: Not described	Three mailings over 6 months	5-item adherence behavioral survey (0-5, lower score indicates better adherence)	Self-report	Baseline: G1: NR G2: NR 95% CI, NR p>0.05	6 months: G1: NR G2: NR 95% CI, NR p>0.05	12 months: G1: NR G2: NR 95% CI, NR p<0.01 18 months: G1: NR G2: NR 95% CI, NR p<0.001
	Powell et al., 1995[97] Overall G1: 1,993 G2: 2,253 Benazepril G1: 175 G2: 243 Metoprolol G1: 830 G2: 898	Adults on benazepril, metoprolol, simvastatin or transdermal estrogen HMO members	G1: Mailed educational videotapes to improve adherence G2: Did not receive mailed videotapes	One mailed video	Medication possession ratio	Pharmacy refill data	NR	9 months: Overall Mean (SD) G1:0.70(0.23) G2:0.70(0.28) 95% CI, NR p: NR On benazepril Mean (SD) G1:0.71(0.25) G2:0.72(0.26) 95% CI, NR p: NR On metoprolol Mean (SD) G1:0.74(0.27) G2:0.73(0.28) 95% CI, NR p: NR	NR
					Percentage with ≥80% adherence by MPR	Pharmacy refill data	NR	9 months: Overall: N (%) G1:917 (46%) G2:998 (44%) 95% CI, NR p: NR On benazepril	NR

Table 17. Hypertension: detailed medication adherence outcomes (continued)

Study	N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Education and behavioral support (continued)								N (%) G1: 78 (45%) G2: 104 (44%) 95% CI, NR p: NR On metoprolol N (%) G1:438 (53%) G2:466 (52%) 95% CI, NR p: NR	
Education (face-to-face, pharmacist)	Lee et al., 2006[78] G1: 83 G2: 76	Adults ≥65 taking ≥4 daily medications Pharmacy at U.S. military medical center	G1: Continuation of intervention: face-to-face educational pharmacist visits and blister packaging of medications G2: Discontinuation of intervention, medications provided in bottles	Seven face-to-face visits over 12 months	Percentage of pills taken vs. prescribed	Pill count	NR	6 months: Mean (SD) G1: 95.5% (7.7) G2: 69.1% (16.4) 95% CI, NR p<0.00	NR
					Percentage with ≥80% adherence	Pill count	NR	6 months: G1: 97.4% G2: 21.7% 95% CI, NR p<0.001	NR
	Solomon et al., 1998[111,112] G1: 62 G2: 70	Adults with HTN (on dihydro-pyridine or dihydro-pyridine + diuretic therapy) Pharmacy at VA medical centers, university hospital	G1: Five face-to-face educational pharmacist visits G2: Two pharmacist visits with only usual care provided	Five face-to-face visits over 6 months	Adherence on Morisky scale (0 to 4, lower score indicates better adherence)	Self-report	Baseline: Mean (SD) G1: 0.63 (0.111) G2: 0.60 (0.087) 95% CI, NR p: 0.75	4 to 6 months: Mean (SD) G1: 0.23 (0.054) G2: 0.61 (0.094) 95% CI, NR p: 0.007 Within-group change from baseline to 4 to 6 months: G1: -0.4 95% CI, NR p<0.05 G2: +0.01 95% CI, NR p: NR	NR

Table 17. Hypertension: detailed medication adherence outcomes (continued)

Study	N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Education (face-to-face, pharmacist) (continued)	Vivian et al., 2002[113] G1: 26 G2: 27	Adults >18 on medication for HTN Pharmacy at VA medical center	G1: Face-to-face pharmacist visits for management of HTN medication, education and counseling G2: Usual care, no face-to-face pharmacist visits	Six face-to-face visits over 6 months	Percentage that forget to take medications ≥1 time/week, survey (0 to 100%)	Self-report	NR	6 months: G1: 68% G2: 48% 95% CI, NR p: 0.252	NR
					Percentage that stop medications when feeling better ≥1 time/week, survey (0 to 100%)	Self-report	NR	6 months: G1: 32% G2: 20% 95% CI, NR p: 0.520	NR
					Percentage that stop medications when they think it is making them feel worse , ≥1 time/week survey (0 to 100%)	Self-report	NR	6 months: G1: 40% G2: 20% 95% CI, NR p: 0.217	NR
					Percentage that take more medication than prescribed when it does not seem to be working ≥1 time/week survey (0 to 100%)	Self-report	NR	6 months: G1: 8% G2: 8% 95% CI, NR p: 1.00	NR
					Percentage that forgot to take medications when away from home overnight, ≥2 time/week survey (0 to 100%)	Self-report	NR	6 months: G1: 15% G2: 10% 95% CI, NR p: 1.00	NR

Table 17. Hypertension: detailed medication adherence outcomes (continued)

Study	N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Education (face-to-face, pharmacist) (continued)	Vivian et al., 2002[113] (continued)				Percentage that received refills for HTN meds within 2 weeks of scheduled refill date	Pharmacy refill data	NR	6 months: G1: 85% G2: 93% 95% CI, NR p>0.42	NR
		Adults >21 with diabetes mellitus and HTN Primary care clinics	G1: Nurse-delivered face-to-face educational session in presence of patient's social support person; educational mailings G2: Same as G1 intervention G3: Same as G1 with exception of not involving patient's social support person for face-to-face education	One face-to-face visit	Adherence level, Morisky scale (low, medium, high)	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	12 months: High (%): G1: NR G2: NR G3: NR Medium (%): G1: NR G2: NR G3: NR Low (%): G1: NR G2: NR G3: NR 95% CI, NR p: NS	NR
		Adults ≥ 55 with HTN Primary care clinic at VA medical center	G1: Personalized risk communication about CHD and stroke. G2: Nonpersonalized educational materials about CHD and stroke	One face-to-face visit	High adherence on Morisky scale	Self-report	Baseline: G1: 50% G2: 51% 95% CI, NR p: NR	3 months: G1: 46% G2: 49% 95% CI, NR p=0.55	NR

Abbreviations: ACE = angiotensin-converting enzyme; BP =blood pressure; CI = confidence interval; CHD = coronary heart disease; G = group; HMO = health maintenance organization; HTN = hypertension; MEMS = medication event monitoring system; MPR = medication possession ratio; N = number; NR = not reported; NS = not significant; PCP = primary care practitioner; rxs = prescriptions; SD = standard deviation; TLC = telephone-linked computer; VA = Department of Veterans Affairs.

Table 18. Hypertension: strength of evidence for blister packaging of medication intervention

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Hypertension blister packaging vs. usual care	1; 93 (85)	Medication adherence	RCT Low	Unknown	Direct	Precise	MPR: Stat sig 6 percentage points difference between groups, Low
	1; 93 (85)	Medication persistence	RCT Low	Unknown	Direct	Precise	Percentage of patients who had prescriptions refilled on time: stat sig 14.3 percentage points difference between groups, Low
	1; 93 (85)	Morbidity: SBP + DBP	RCT Low	Unknown	Direct	Imprecise	No stat sig difference in change in SBP or DBP or in percentage of patients with reduced SBP 29.8 percentage points difference in patients with reduced DBP at 12 months in G1 than G2, stat sig Insufficient
	1; 93 (85)	Morbidity: Angina, MI, or stroke	RCT Low	Unknown	Direct	Imprecise	No stat sig difference between groups for angina, MI, or stroke Insufficient
	1; 93 (85)	Health care utilization: ED visits + hospitaliza-tions	RCT Low	Unknown	Direct	Imprecise	No stat sig difference between groups for either outcome Insufficient

Abbreviations: DBP = diastolic blood pressure; ED = emergency department; G = group; MI = myocardial infarction; MPR = medication possession ratio; RCT = randomized controlled trial; SBP = systolic blood pressure; stat sig = statistically significant

Detailed Synthesis for Case Management for Hypertension

Medication Adherence

Among the three trials with interventions involving case management, two found evidence for improved medication adherence (Table 17).[101-103] Both trials with adherence improvements used MEMS caps to measure adherence. In one in patients with depression and hypertension, the number of with $\geq$80% adherence to hypertension medications was higher in the intervention than control group at 6 weeks.[101] In the other trial involving nurse case management for hypertension, the mean adherence to taking daily medications was higher in the intervention than the control group at 6 months.[102] In the trial that did not find improved adherence, Morisky scale scores did not differ between groups at 6 months, although improved Morisky scores were noted in all groups.[103] We graded strength of evidence as low for adherence benefit (Table 19).

Other Outcomes

Both trials found improvements in systolic and diastolic blood pressure outcomes in the intervention group compared with the control group. In one trial, the mean systolic blood pressure was approximately 14 mm Hg lower in the intervention arm than the control arm at 6 weeks (127.3 mm Hg vs. 141.3 mm Hg, p=0.003); in addition, the mean diastolic blood pressure was approximately 9.2 mm Hg lower in the intervention arm than in the control arm at 6 weeks (75.8 mm Hg vs. 85.0 mm Hg, p=0.002).[101] In the other trial, systolic blood pressure decreased from baseline to 6 months by approximately 8.5 mm Hg more in the intervention arm than in the control arm (-14.2 mm Hg vs. -5.7 mm Hg, p<0.01); diastolic blood pressure decreased from baseline to 6 months by approximately 3.1 mm Hg more in the intervention arm than in the control arm (-6.5 mm Hg vs. -3.4 mm Hg, p<0.05).[102] We graded the strength of evidence as low for blood pressure benefit (Table 19).

Table 19. Hypertension: strength of evidence for case management interventions

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Hypertension case management vs. usual care	3; 516 (64 + NR in 2 trials)	Medication adherence	RCT Medium	Consistent	Direct	Precise	Two of three RCTs with stat sig difference in adherence: (1) MEMS ≥80% adherence: 46.8 percentage points more in G1 than G2 (2) MEMS adherence, mean: 11.3 percentage points higher in G1 than G2 Low
	2; 214 (64 + NR in 1 trial)	Morbidity: SBP + DBP	RCT Medium	Consistent	Direct	Precise	Two RCTs with stat sig difference in SBP between G1 and G2 : (1) - 14 mm Hg difference (2) - 8.5 mm Hg difference Low Two RCTs with stat sig difference in DBP between G1 and G2 : (1) - 9.2 mm Hg difference (2) -3.1 mm Hg difference Low

Abbreviations: DBP = diastolic blood pressure; G = group; MEMS = medication event monitoring system; NR = not reported; pts = patients; RCT = randomized controlled trial; SBP = systolic blood pressure; stat sig = statistically significant.

Detailed Synthesis for Collaborative Care for Hypertension

Medication Adherence

Of the three trials that evaluated collaborative care interventions, none found improvements in medication adherence for hypertension medications (Table 17).[89,104,105] One trial found no

difference in Morisky scores between groups at 6 months;[104] another found no difference in Morisky scores at 12 months;[105] and a third found no difference between groups either in the percentage of days nonadherent to ACE inhibitors or in the adjusted difference in percentage of nonadherent days to ACE inhibitors between groups at 12 months.[89] We graded strength of evidence as low for no benefit from collaborative care (Table 20).

Table 20. Hypertension: strength of evidence for collaborative care interventions

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Hypertension collaborative care vs. usual care	3; 1194 (785)	Medication adherence	RCT Medium	Consistent	Direct	Imprecise	No stat sig differences between groups Low

Abbreviations: RCT = randomized controlled trial; stat sig = statistically significant.

Detailed Synthesis for Education and Behavioral Support for Hypertension

Medication Adherence

Of the five trials that evaluated education and behavioral support delivered by telephone, mail, and/or video,[97,106-110] two trials used self-reported Morisky scales,[106-108] one used pill counts[109], one used both a self-reported behavioral measure of nonadherence and a stage-of-change assessment for medication adherence,[110] and one used MPRs from pharmacy refill data.[97] Two trials found improved adherence outcomes in the intervention arm compared with the control arm (Table 17).[109,110] In one trial, groups did not differ in an unadjusted model evaluating the change in proportion of medications (pill counts) taken from baseline to 6 months but did differ significantly after adjustments for age, sex, baseline medication adherence, and baseline adherence by treatment group.[109] In the other trial, adherence improved significantly as assessed by 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.[110] Among the three trials that did not find improved adherence outcomes, two found no difference between groups for the proportion reporting high adherence on Morisky scales at 6 months.[106-108] The third trial did not find improved MPRs in the intervention group compared with the control group either among the overall trial population or among those with a prescription for benazepril or metoprolol.[97]

Given the variable findings for medication adherence, measure variability, and outcome imprecision, we graded the strength of evidence as low for benefit of these types of interventions (Table 21).

Other Outcomes

Of the two trials that identified improved medication adherence, one reported additional blood pressure measures but did not find any significant differences between intervention and control groups for change in systolic blood pressure (11 mm Hg vs. 10.6 mm Hg, p=0.85) or diastolic blood pressure (5.4 mm Hg vs. 3.3 mm Hg, p=0.09) from baseline to 6 months (insufficient evidence) (Table 21).[109]

Table 21. Hypertension: strength of evidence for education and behavioral support (phone, mail, and/or video) interventions

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Hypertension education and behavioral support vs. usual care	5; 6996 (5149 + NR in 2 trials)	Medication adherence, overall (all measures)	RCT Medium	Consistent	Direct	Imprecise	Multiple variable outcomes Two RCTs with stat sig difference in adherence: (1) 6 percentage points more change in % pills taken in G1 than G2 from baseline to 6 months (2) More in G1 than G2 reporting adherence at 12 and 18 months, no numbers reported Low
	1; 299 (267)	SBP	RCT Medium	Unknown	Direct	Imprecise	No stat sig difference between groups in change from baseline to 6 months Insufficient
	1; 299 (267)	DBP	RCT Medium	Unknown	Direct	Imprecise	No stat sig difference between groups in change from baseline to 6 months Insufficient

Abbreviations: DBP = diastolic blood pressure; G = group; NR = not reported; RCT = randomized controlled trial; SBP = systolic blood pressure; stat sig = statistically significant.

Detailed Synthesis for Education for Hypertension

Medication Adherence

In the three trials of educational interventions that included face-to-face pharmacist visits,[78,111-113] two found significantly improved medication adherence (Table 17).[78,111,112] One trial (using pill counts) found that the percentage of pills taken versus prescribed and the proportion of participants with ≥80% adherence were both higher in the intervention than the control arm over 6 months.[78] The other trial (Morisky scores) found significantly higher scores in the intervention arm than the control arm at the followup visit between 4 and 6 months;[111,112] within-group Morisky score improvements were noted in the intervention arm from baseline to followup.[111,112] The trial that used self-reported survey questions to assess medication adherence and pharmacy refill data to assess medication persistence did not find improved medication adherence over 6 months.[113] Given the variable findings for improved adherence, measure variability, and outcome imprecision, we graded the strength of evidence as low for benefit (Table 22).

Table 22. Hypertension: strength of evidence for education (face-to-face with pharmacist) interventions

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Hypertension education (face-to-face with pharmacist) discontinuation of or less intense intervention	3; 348 (344)	Medication adherence	RCT Medium	Consistent	Direct	Imprecise	Variable outcomes, some stat sig differences favoring intervention Low
	1; 56 (53)	Medication persistence	RCT Medium	Unknown	Direct	Imprecise	No difference between groups refilling meds on time Insufficient
	2; 292 (268)	SBP	RCT Medium	Consistent	Direct	Precise	-6.4 or -8.9 mm Hg mean SBP difference (stat sig G1 vs. G2) in two studies Moderate
	2; 292 (268)	DBP	RCT Medium	Consistent	Direct	Imprecise	-1.1 or -4.4 mm Hg mean DBP difference (G1 vs. G2) in two trials Insufficient
	1, 133 (NR)	Quality of life	RCT Medium	Unknown	Indirect	Imprecise	No statistically significant differences for sexual dysfunction, dizziness and headaches Insufficient
	1; 133 (130)	Patient satisfaction	RCT Medium	Unknown	Indirect	Precise	Stat sig improvement in four of five questions Low
	1; 133 (124)	Health care utilization: hospital visits	RCT Medium	Unknown	Direct	Precise	0.08 fewer hospital visits in intervention group Low
	1; 133 (124)	Health care utilization: contacts with other health care providers	RCT Medium	Unknown	Direct	Precise	0.41 fewer visits in intervention group Low
	1; 133 (124)	Health care utilization: ER visits	RCT Medium	Unknown	Direct	Imprecise	Insufficient

Abbreviations: DBP = diastolic blood pressure; ER = emergency room; G = group; Hosp = hospital; mm Hg = millimeter mercury; RCT = randomized controlled trial; SBP = systolic blood pressure; stat sig = statistically significant; vs. = versus.

Other Outcomes

Both trials that reported improved medication adherence reported various blood pressure measures.[78,111,112] Both found improvements in mean systolic blood pressure. In one trial, the mean systolic blood pressure at 14-month followup was 124.4 mm Hg in the intervention group and 133.3 mm Hg in the control group (p=0.005), with an approximate difference between groups of 8.9 mm Hg.[78] The difference in systolic blood pressure between baseline (i.e., after 2-month run-in) and at 14-month followup in this trial was -6.9 mm Hg in the intervention group and -1.0 mm Hg in the control group (p=0.04). In the second trial, the mean systolic blood

pressure measured at between 4 and 6 months was 138.5 mm Hg in the intervention group and 144.9 mm Hg in the control group (p=0.044), with an approximate difference between groups of 6.4 mm Hg.[111,112] Mean systolic blood pressure declined significantly in the intervention group between baseline and 4- to 6-month followup by approximately 8.2 mm Hg (146.7 mm Hg to 138.5 mm Hg, p<0.01). The decline in mean systolic blood pressure from baseline to the same followup points was not significant in the control group (146.2 mm Hg to 144.9, p not reported). The magnitude of effect was consistent for systolic blood pressure between the two trials and outcomes were precise, so we graded the strength of evidence as moderate for benefit on this outcome (Table 22).

By contrast, in these two trials, diastolic blood pressures did not drop significantly for either group and were not significantly different between groups at followup, although this measure would be anticipated to change less than systolic blood pressure in response to treatment. Because the magnitude of effect was not significant and outcomes were imprecise, we graded the strength of evidence as insufficient for this outcome.

Quality of life was evaluated in one pharmacist intervention trial.[111,112] Quality-of-life items included problems with sexual functioning, feeling dizzy upon standing up, and having headaches more than usual, none of which differed significantly between groups at followup (between 4 and 6 months).[111,112] Of note, the proportion of intervention patients reporting problems with sexual functioning during the prior 4 weeks changed significantly from baseline to followup at between 4 and 6 months (34.0% at baseline and 2.5% at followup, p=0.003).

Patient satisfaction reported in one trial[111,112] consisted of answers to individual questions from a pharmaceutical care questionnaire.[15,17] We abstracted data for only five items that directly applied to a patient's experience with medications for the disease for which medications had been prescribed. Questions were rated on a Likert scale (1 strongly agree; 5 strongly disagree). The intervention group scored significantly favorably compared with the control group in four questions in which they were asked about feeling secure about taking medications (1.39 vs. 1.69, p=0.004) , understanding their illness (1.45 vs. 1.84, p=0.002), feeling that the pharmacist gave complete explanations about their medication (1.48 vs. 1.82, p=0.006), and feeling that the pharmacist should give more complete explanations about medications (4.16 vs. 3.81, p=0.042).[15,17] We graded strength of evidence as low for evidence of benefit (Table 22).

Health care utilization measures were self-reported in one pharmacist education trial.[111,112] Significantly fewer hospitalizations and fewer contacts with health care providers other than pharmacists occurred over 4 weeks in the intervention arm than the control arm; the groups did not differ 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 trial. We graded the strength of evidence related to hospitalizations and contacts with health care providers other than pharmacists as low for evidence of benefit and evidence related to emergency room visits as insufficient because of imprecision (Table 22).

Education With Social Support for Hypertension

Medication Adherence

The trial 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 scale at 12 months (insufficient evidence) (Table 23).[91]

Table 23. Hypertension: strength of evidence for education with social support interventions

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Hypertension education with social support vs. education without social support	1; 199 (199)	Medication adherence	RCT Medium	Unknown	Direct	Imprecise	No stat sig differences between groups at 12 months Insufficient

Abbreviations: RCT = randomized controlled trial; stat sig = statistically significant.

Detailed Synthesis for Risk Communication for Hypertension

Medication Adherence

The trial evaluating the effect of risk communication about coronary heart disease and stroke to participants did not find improved adherence in the intervention groups as measured with the Morisky scale at 3 months (insufficient evidence) (Table 24).[114]

Table 24. Hypertension: strength of evidence for risk communication

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Hypertension risk communica-tion vs. educational materials	1; 89 (89)	Medication adherence	RCT Medium	Unknown	Direct	Imprecise	No stat sig difference between groups at 3 months Insufficient

Abbreviations: RCT = randomized controlled trial; stat sig = statistically significant.

Key Question 1. Heart Failure: Medication Adherence Interventions

Description of Included Studies

Overview

We identified four trials that evaluated interventions to improve medication adherence among patients with heart failure.[115-118] We rated three as medium risk of bias[115,117,118] and one as low risk of bias.[116]

Population

All trials were conducted in adults ranging from ages 18 and older[118] to ages 70 and older;[117] participant ages ranged from a mean of 55 to 57 years of age[118] to a median age of 80 years.[117] Between 20 percent to 26 percent[118] and 66 percent to 68 percent[116,117] of the trial populations were women. Black participants made up from 23 percent to 33 percent[115] and 45 percent to 52 percent[116] of the trial populations in the two trials that reported this information.

Intervention

The four trials tested diverse interventions all targeted at patients; three additionally targeted systems of care.[116-118] One trial had two intervention arms and one control arm.[115] In this trial, a research assistant made video calls via provided equipment to persons in one intervention arm and telephone calls to individuals in the other arm; all calls reminded participants to take their medications daily.[115] Another trial evaluated a multicomponent pharmacist-led intervention that provided participants with face-to-face education, literacy-sensitive written materials, and labeling of medications with icons to promote adherence.[116] The third trial examined a case management intervention with the following components: as inpatients, patients received nurse-delivered education that focused on adherence, visits from a dietitian and social worker, and medication review by a geriatric cardiologist; following discharge, personnel from home care services visited patients at home and the trial nurse telephoned patients.[117] The final trial 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.[118]

Comparator

Active arms were compared with usual care in all four trials. In the trial of video and telephone call reminders, the control group did not receive any calls.[115] In the multicomponent pharmacist-led intervention, the control group had no contact with the intervention pharmacist beyond an initial visit to obtain medication history.[116] In the case management trial, control participants received conventional care from their regular physician and standard hospital and discharge services.[117] In the trial of access to online medical records, the control group had no access to online records; they received the same educational guide for heart failure as the intervention arm, but as a printed packet instead of an online document.[118]

Outcomes

None of the trials reported on persistence or initiation of medication. Measures of adherence included MEMS caps in two trials,[115,116] self-reported measures in two trials (Morisky scale and adherence questionnaire),[116,118] and pharmacy refill data[116] or pill counts[117] in one trial each. One trial used multiple measures of adherence (MEMS caps, pharmacy refill data, and self-reported adherence).[116]

Three trials reported additional outcomes. Two trials reported quality-of-life measures: the Minnesota Living with Heart Failure (MLHF) and the SF-36 questionnaires in one trial,[115] and the Chronic Heart Failure questionnaire in the other trial.[116] One trial reported patient satisfaction outcomes using a self-reported validated questionnaire.[116] All-cause emergency department (ED) visits were reported in one trial[116,118] and all-cause hospitalizations in two.[116-118] Among the two trials reporting all-cause hospitalizations, one reported both the number of patients hospitalized and total number of hospitalizations,[117,118] and one additionally reported total hospitalization days.[117] One trial 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.[116] One trial evaluated costs (inpatient, outpatient, and combined).[116]

Timing

The shortest trial lasted 1 month[117] and the longest 12 months.[118] One trial reported adherence outcomes both during and at the conclusion of the intervention.[118] The other three trials reported adherence outcomes at the conclusion of the intervention.[115-117] Two trials additionally reported adherence outcomes after interventions had concluded: one at 2 weeks following an intervention,[115] and one in 3 months following completion of an intervention.[116]

ED visits and hospitalizations were reported for a 12-month period in the trial with a 9-month intervention followed by a 3-month postintervention evaluation period.[116] In a trial with a 30-day intervention, ED visits and hospitalizations were reported for 90 days.[117] The period of evaluation was unclear in the remaining trial that reported ED visits and hospitalizations.[118]

The trial with costs and patient satisfaction outcomes reported these measures for 12 months; it reported quality of life at 6 and 12 months.[116]

Setting

One trial focused on a population recruited from an urban home health agency and ambulatory care clinic.[115] Three trials focused on populations cared for in a university-affiliated system: one recruited patients from an academic primary care practice and an urban hospital;[116] one recruited patients admitted to a university teaching hospital with a heart failure exacerbation;[117] and one recruited patients from a heart failure specialty clinic.[118]

Interventions took place in diverse settings: patient homes,[115] a pharmacy,[116] both inpatient and outpatient settings,[117] and within a heart failure specialty clinic.[118]

Applicability

Notable limitations to applicability included the following: a low participation rate (10 percent) among those eligible in one trial;[115] 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 trial;[118] and the high complexity of one intervention that involved at least four disciplines of health professionals and both inpatient and outpatient components.[117] Each trial targeted different age groups. Participants were the youngest (mean age approximately 56 years) in the trial of Web-based access to medical records;[118] participants in the multicomponent pharmacist-led trial were somewhat older (mean age approximately 62 years);[116] the other two trials were conducted in older age groups with a mean age of approximately 75 years in the trial of reminder video and telephone calls[115] and a median age of 80 years in the case management trial.[117] Thus, the final two trials would be more generalizable to elderly patients with heart failure. All trials were based primarily in nonrural settings, so would have limited generalizability for rural settings.

Key Points

- Three of four trials found evidence suggestive of improved medication adherence (Table 25).
- No trials produced evidence of sustained adherence improvements following the end of the interventions; no trial evaluated outcomes beyond 3 months after the intervention ended.
- Because the components of the four interventions were so heterogeneous, we evaluated each separately for strength of evidence.
- Health care utilization results were inconsistent across the trials.

Table 25. Heart failure: summary of findings

Type of Intervention	Study	Adherence: Measure, Followup Period Overall Result (+/=/-) and Timing	Additional Outcomes: Outcome Overall Result (+/=/-) and Timing
Reminder video and telephone calls	Fulmer et al., 1999[115] N=60	+ Adherence rate, 8 weeks	= Quality of life at 10 weeks
Multicomponent pharmacist-led	Murray et al., 2007[116]	+ Adherence for taking and scheduling medications, during 9-month intervention = Adherence for taking and scheduling medications, during 3 months following intervention + Medication possession ratio over 1 year = Self-report at 9 months	= Quality of life at 6 months = Quality of life at 12 months = Patient satisfaction at 12 months + Combined all-cause ED visits; hospitalizations over 12 months = All-cause hospitalization, combined cardiovascular ED visits and hospitalization; combined heart failure ED visits and hospitalizations over 12 months = Outpatient health care costs; inpatient health care costs; combined outpatient and inpatient costs over 12 months
Case management	Rich et al., 1996[117] N=156	+ Percentage of pills taken correctly, proportion with ≥80% medication compliance, and proportion with ≥90% medication compliance over 30 days	= Health care utilization (over 90 days): number of patients with all-cause readmissions; number of all-cause readmissions; days hospitalization from all-cause readmissions
Access to medical records	Ross et al., 2004[118] N=107	= Morisky scores at 6 and 12 months	NA

Abbreviations: (+) = statistically significant difference favoring intervention arm(s); (=) = no statistically significant difference, (-) = statistically significant difference favoring comparison arm; ED = emergency department; N = number.

Reminder Intervention (Video and Telephone Calls)

- Medication adherence: One trial with limited followup reported improved medication adherence (low strength of evidence for benefit).
- Quality of life: This trial found no evidence of significant differences between trial arms at followup on two measures of quality of life (insufficient evidence).

Multicomponent, Pharmacist-Led Intervention

- Medication adherence: Medication adherence was better in the intervention group than control group on objective measures (MEMS caps, pharmacy refill data), but not on a self-reported measure during the 9-month intervention (low strength of evidence of benefit at 9 months). This trial did not show evidence that the intervention effect was sustained in the 3 months after the intervention (at 12-month followup, loss of all significant differences between groups (insufficient evidence of longer benefit).
- Quality of life: Disease-specific quality of life did not differ significantly between intervention and control groups at two time points (insufficient evidence).
- Patient satisfaction: The intervention group had better patient satisfaction outcomes than the control group (low strength of evidence of benefit).

- Health care utilization: The trial demonstrated evidence of benefit for all-cause ED visits and combined all-cause ED and hospitalization (low strength of evidence); however, it provided no evidence of benefit for all other health care utilization measures, including all-cause hospitalizations, combined cardiovascular ED visits and hospitalizations, and combined heart failure-related ED visits and hospitalizations (insufficient evidence).
- The trial demonstrated no benefit for inpatient costs, outpatient costs, and combined inpatient and outpatient costs (insufficient evidence).

Case Management (Multisetting, Multidisciplinary Intervention)

- Medication adherence: This relatively small trial demonstrated evidence of short-term (30-day) benefit (low strength of evidence).
- Health care utilization: Groups did not differ on several measures of all-cause readmissions (number of patients with readmissions, number of readmissions, and days of hospitalization from readmissions) (insufficient evidence).

Access to Medical Records

- Medication adherence: This trial showed no differences between groups on Morisky scales at 6 and 12 months (insufficient evidence of benefit).
- Other outcomes: Mortality, quality of life, patient satisfaction, all-cause hospitalizations, ED visits, and heart failure-related visits did not differ between groups (insufficient evidence).

Detailed Synthesis for Video and Telephone Reminder Intervention for Heart Failure

Medication Adherence

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 26 and Table 27) (low strength of evidence of benefit).[115] The control group decline in adherence from baseline (81 percent) to followup (57 percent) made up much of the difference between intervention and control groups (Table 26).

Other Outcomes

The Minnesota Living with Heart Failure (MLHF) questionnaire is a 21-item scale with each item scored 0 to 5 (a lower score indicates lower impact of heart failure treatment on quality of life). MLHF scores did not differ for intervention and control groups at 10 weeks but they improved significantly in all groups from baseline to 10 weeks (G1, video: 43.1 to 36.7 (-6.4); G2, phone: 54.4 to 32.9 (-21.5), G3 control: 46.4 to 32.9 (-13.5); $p<0.001$ for all within-group improvements (insufficient evidence, Table 27).[115] Scores from the SF-36 questionnaire did not differ between groups at 10 weeks and did not change significantly in any group from baseline to followup (insufficient evidence, Table 27).[115]

Table 26. Heart failure: detailed medication outcomes

Type of Intervention	Study N per Group	Sample and Setting	Intervention Groups	Intervention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Reminder calls	Fulmer et al., 1999[115] G1: 17 G2: 15 G3: 18	Adults >65 with HF Urban Ambulatory	G1: Daily video reminder G2: Daily phone reminder G3: No reminder calls	Daily calls (Mon-Fri), 6-week duration	Compliance rates (0 to 100%, % of total pills taken)	MEMS	G1: 82% G2: 76% G3: 81%	8 weeks: G1: 84% G2: 74% G3: 57% (p<0.04) 95% CI, NR G1 + G2 vs. G3: F=4.08, p<0.05 G1 vs. G2:p>0.05	NR
Multicomponent pharmacist-led	Murray et al., 2007[116] G1: 122 G2: 192 Morisky and MPR outcomes G1: NR G2: NR	Adults ≥50 with HF Pharmacy	G1: Pharmacist-delivered verbal and written instructions, medication labeling with icons G2: No contact with intervention pharmacist after initial medication history	Number of face-to-face visits not totaled, 9-month duration	Taking adherence: Percentage of prescribed doses taken (0 to 100%, total percentage of pills taken)	MEMS	NR	9 months during intervention: 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: NR	3 months following intervention: 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
					Scheduling adherence: Adherence to medication dose timing (0 to 100%, total percentage of pills taken within a similar time frame)	MEMS	NR	9 months during intervention: 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	3 months following intervention: 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

Table 26. Heart failure: detailed medication outcomes (continued)

Type of Intervention	Study N per Group	Sample and Setting	Intervention Groups	Intervention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Multicomponent pharmacist-led (continued)					MPR (0 to 100%, prescriptions prescribed to prescriptions received)	Pharmacy refill records	NR	1 year: G1: 109.4% G2: 105.2% Difference: 4.2% 95% CI, NR p=0.007	NR
					Change in median of composite scores from Morisky and other validated questionnaire (range NR)	Self-report	NR	Change in median score from baseline to 9 months: G1: 1.0 G2: 0.8 95% CI, NR p=0.48	NA
Case management	Rich et al., 1996[117] G1: 80 G2: 76	Adults ≥70 admitted with HF University teaching hospital	G1: Multidisciplinary intervention (inpatient and outpatient): HF teaching, med review, home care visits and phone contact by nurse G2: Standard hospital services (teaching and med instructions)	Visits not totaled, 30-day duration	Percentage of pills taken correctly for each current medication averaged (method #1)	Pill count	NR	30 days after discharge: G1: 87.9% (SD 12.0) G2: 81.1% (SD 17.2) 95% CI, NR p=0.003	NR
					Proportion with ≥80% medication compliance by method #1	Pill count	NR	30 days after discharge: G1: 85.0% G2: 69.7% 95% CI, NR p=0.036	NR
					Percentage of pills taken correctly for all current medications, pooled (method #2)	Pill count	NR	30 days after discharge: G1: 87.5% (SD 12.6) G2: 80.9% (SD 16.7) 95% CI, NR p=0.003	NR

Table 26. Heart failure: detailed medication outcomes (continued)

Type of Intervention	Study N per Group	Sample and Setting	Intervention Groups	Intervention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Case management (continued)					Proportion with ≥80% medication compliance by method #2	Pill count	NR	30 days after discharge: G1: 82.5% G2: 66.2% 95% CI, NR p=0.033	NR
					Proportion with ≥90% medication compliance, unclear if method #1 or #2 used	Pill count	NR	30 days after discharge: G1: 56.3% G2: 34.2% 95% CI, NR p=0.032	NR
Access to medical records	Ross et al., 2004[118] G1: NR G2: NR	Adults ≥18 with HF HF clinic	G1: Access to online medical record, educational guide for HF, and messaging system with nursing staff. G2: No access to online medical record or messaging system; printed HF educational guide	Visits not totaled, 12 months	Morisky score (0 to 4 points, higher score indicates better adherence)	Self-report	NR	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

Abbreviations: CI = confidence interval; F = F-statistic; G = group; HF = heart failure; MEMS = medication event monitoring system; MPR = medication possession ratio; NR = not reported; SD = standard deviation.

Table 27. 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 vs. no reminder calls	1; 60 (50)	Medication adherence	RCT Medium	Unknown	Indirect	Precise	Difference of 17 to 27 percent comparing video and phone to control in MEMS adherence over 8 weeks Low
	1; 60 (42)	Quality of life	RCT Medium	Unknown	Direct	Imprecise	No statistically significant difference Insufficient

Abbreviations: MEMS = medication event monitoring system; RCT = randomized controlled trial

Detailed Synthesis for Multicomponent Pharmacist-Led Intervention for Heart Failure

Medication Adherence

In a multicomponent pharmacist-led intervention, MEMS caps adherence measures of "taking adherence" (percentage 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) than in the control group (67.9 percent taking and 47.2 percent scheduling adherence) at the end of a 9-month intervention (Table 26 and Table 28, low strength of evidence for benefit at 9 months).[116] However, when the same outcomes were measured 3 months following completion of the intervention, differences between the intervention and control groups were no longer significant. The MPR (pharmacy refill data) was significantly higher in the intervention group (109.4 percent) than in the control group (105.2 percent) over 1 year (insufficient evidence).[116] Self-reported adherence did not differ between intervention and control groups at 9 months (insufficient evidence, Table 28).[116]

Other Outcomes

Questionnaire-based Heart Failure quality-of-life data did not differ significantly between groups for changes from baseline to 6 or 12 months (insufficient evidence, Table 28).[116] This trial reported patient satisfaction with pharmacy services with a 12-item validated instrument; improvement from baseline to 12 months was significant in the intervention group compared with the control group (score improvements of 1 vs. 0.7, p=0.02) (low strength of evidence for benefit).[116] This trial found significantly fewer all-cause ED visits (incidence rate ratio [IRR] 0.82, 95% CI, 0.70, 0.95) and combined all-cause ED visits and hospitalizations (IRR, 0.82, 95% CI, 0.72 to 0.93) over 12 months in the intervention group than in the control group (low strength of evidence for benefit on these measures).[116] Intervention and control groups did not differ significantly for all-cause hospitalizations, combined cardiovascular-related ED visits and hospitalizations, or combined heart failure-related ED visits and hospitalizations over 12 months (insufficient evidence).[116] Finally, outpatient health care costs, inpatient costs, and the sum of inpatient and outpatient costs did not differ significantly between intervention and control groups for the year (insufficient evidence).[116]

Table 28. 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 vs. usual care	1; 314 (314 for MEMS caps, NR for MPR or self-report)	Medication Adherence	RCT Medium	Unknown	Direct	Precise	Stat sig difference in percentage points for taking medication (MEMS) at 9 months: 10.9 Stat sig difference in percentage points for adherence to timing (MEMS) at 9 months: 5.9 Stat sig difference in percentage points for MPR over 12 months: 4.2 No significant difference for self-report Low
	1; 314 (NR)	Quality of life	RCT Medium	Unknown	Direct	Imprecise	No stat sig difference Insufficient
	1; 314 (NR)	Patient satisfaction	RCT Medium	Unknown	Direct	Precise	Stat sig difference between groups of 0.3 on 12-point validated questionnaire Low
	1; 314 (314)	Health care utilization: All-cause ED visits, hosp, and Combined ED visits and hosp	RCT Medium	Unknown	Direct	Precise for all-cause ED visits and all-cause ED+hosp; Imprecise for all-cause hosp	Stat sig difference of 0.52 mean all-cause ED visits and 0.69 mean all-cause ED+hosp between groups Low All-cause hosp: no stat sig difference Insufficient
	1; 314 (314)	Health care utilization: CV-related and HF-related events	RCT Medium	Unknown	Direct	Imprecise	No stat sig difference Insufficient
	1; 314 (314)	Costs	RCT Medium	Unknown	Direct	Imprecise	No stat sig difference Insufficient

Abbreviations: CV = cardiovascular; ED = emergency department; HF = heart failure; hosp = hospitalization; MEMS = medication event monitoring system; MPR = medication possession ratio; NR = not reported; RCT = randomized controlled trial; stat sig = statistically significant.

Detailed Synthesis for Case Management for Heart Failure

Medication Adherence

In the trial of a multidisciplinary, multisetting intervention, pill count measures were used to derive multiple measures of adherence, including the percentage of medications taken correctly (averaged by medication and pooled overall) and the proportion of participants with ≥80 percent adherence and ≥90 percent adherence (Table 26).[117] All measures improved significantly in the

intervention group compared with the control group at 30-day followup (low strength of evidence of benefit) (Table 29).[117]

Table 29. Heart failure: strength of evidence for case management

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Heart failure case management: multidisciplinary, multisetting intervention vs. usual care	1; 156; (156)	Medication adherence	RCT Medium	Unknown	Direct	Precise	Stat sig difference in percentage points for med adherence between groups: 6.6 to 6.8 (range), pill count over 30 days Stat sig difference in percentage points for proportion with ≥80% adherence between groups: 15.7 to 16.3, pill count over 30 days Low
	1; 156 (156)	Health care utilization: All-cause hospital readmission	RCT Medium	Unknown	Direct	Imprecise	No significant difference in multiple measures of all-cause readmission Insufficient

Abbreviations: med = medication; RCT = randomized controlled trial; stat sig = statistically significant.

Other Outcomes

This trial 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 (insufficient evidence) (Table 29).[117]

Detailed Synthesis for Access to Medical Records for Heart Failure

Medication Adherence

In the trial in which access to an online medical record was provided to the intervention group, self-reported Morisky scores were collected at 6 and 12 months (Table 26).[118] The groups did not differ on the Morisky scores at 6 or 12 months (insufficient evidence) (Table 30).

Table 30. Heart failure: strength of evidence for access to computer records

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Heart failure access to computer records vs. usual care	1; 107; (NR)	Medication adherence	RCT Medium	Unknown	Direct	Imprecise	Morisky scores: No significant difference at 6 or 12 months Insufficient

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

Key Question 1. Myocardial Infarction: Medication Adherence Interventions

Description of Included Study

Overview

One trial (medium risk of bias) tested an intervention to improve medication adherence among patients with a recent myocardial infarction.[119]

Population

This trial was conducted in adults ages 18 and older with a mean participant age of approximately 65 years. Women made up approximately 32 percent of the trial population.

Intervention and Comparator

The intervention in this trial was targeted at both patients and providers. The intervention provided education and behavioral support; two mailed communications approximately 2 months apart primarily stressed the importance of using beta blockers following myocardial infarctions. Primary care clinicians caring for patients in the intervention arm received a letter that encouraged their support of the initiative.

In the control arm, neither patients nor their primary care clinicians received these communications.

Outcome and Timing

Medication adherence outcomes (pharmacy refill data) included the absolute increase in proportion of days covered per month from baseline to followup and the likelihood of having ≥80 percent of medications across the entire 9-month period. Medication persistence outcomes (pharmacy refill data) included the proportion of patients with gaps of 1, 2, 3, and 4 months in length between filling beta-blocker prescriptions. The intervention lasted approximately 1 month, which spanned the time between two mailings to patients, and the trial measured adherence and persistence across 9 months.

Setting

This trial was based in primary care clinics.

Applicability

This trial is generally applicable to ambulatory care patients who have suffered a myocardial infarction (more so for men than women) and provides more than just short-term data.

Key Points

- Medication adherence and persistence: In the trial providing education and behavioral support following a myocardial infarction, medication adherence was significantly better in the intervention than the control group at 9 months (Table 31, low strength of evidence for benefit). Intervention and control groups did not differ significantly in persistence (insufficient evidence).

Table 31. Myocardial infarction: summary of findings

Type of Intervention	Studies, N Randomized	Adherence: Measure, Followup Period Overall Result (+/=/-) and Timing	Additional Outcomes: Outcome Overall Result (+/=/-) and Timing
Education and behavioral support	Smith et al., 2008[119] N=907	+ Absolute increase in proportion of days covered over 9 months + Likelihood of having ≥ 80% of days covered over 9 months = Proportion of groups with gaps of 1, 2, 3, or 4 months in refilling beta-blocker	NR

Abbreviation: NR = not reported.

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

The trial involving 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 32).[119] Compared with the controls, patients in the intervention group had a 4.3 percent mean absolute increase in proportion of days covered per month from baseline to 9 months; they had a higher likelihood of having ≥80 percent or more of medications across the entire 9-month period (low strength of evidence for benefit) (Table 33). The groups did not differ in the proportion of patients with gaps of 1, 2, 3, or 4 months between beta-blocker prescriptions (insufficient evidence).

Table 32. Myocardial infarction: detailed medication adherence outcomes

Type of Intervention	Study N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, direction)	Source	Baseline	Followup
Education and behavioral support	Smith et al., 2008[119] G1: 426 G2: 410 Gap in refilling prescription G1: NR G2: NR	Adults ≥18 years with a myocardial infarction Primary care clinics	G1: Two mailings to patients encouraging beta-blocker adherence; mailing to primary care providers G2: Usual care (no mailings)	Two mailings	Absolute increase in proportion of days covered per month	Pharmacy refill data	NR	9 months: G1: 4.3% mean absolute increase in days covered per month compared with G2 95% CI, NR p=0.04
					Likelihood of having at least 80% proportion of days covered	Pharmacy refill data	NR	9 months: G1: 64.8% G2: 58.5% Relative risk: 1.17 95% CI, 1.02 to 1.29
					Among patients with a beta-blocker prescription at start of intervention: Proportion of group with a gap in refilling beta-blocker	Pharmacy refill data	NR	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 33. Medication adherence interventions for myocardial infarction: strength of evidence for education and behavioral support

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Myocardial infarction: Education and behavioral support	1; 907(836)	Medication adherence	RCT Medium	Unknown	Direct	Precise	Stat sig difference in percentage points mean increase in adherence over 9 months: 4.3% Stat sig difference in percentage points with ≥80% adherence: 6% Low
	1; 907(NR)	Medication persistence	RCT Medium	Unknown	Direct	Imprecise	No difference Insufficient

Abbreviations: RCT = randomized controlled trial; stat sig = statistically significant.

Key Question 1. Reactive Airway Diseases: Medication Adherence Interventions

Description of Included Studies

Overview

Eight trials implemented interventions to improve medication adherence among patients with asthma[120-127] or for asthma or COPD.[125] We rated three as having low risk of bias[123,125,126] and five as having medium risk of bias.[120-122,124,127]

Population

Of the eight trials, four did not appear to select for asthma severity or control;[120,124-126] populations for the remaining four were restricted to moderate-to-severe asthma (two trials),[121,123] low-to-moderate severity (one),[122] and poorly controlled asthma (one).[127] One trial presented results separately for asthma and COPD.[125]

Interventions

Five trials 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.[120-124] Three used traditional care settings with nurses and other professionals;[121-123] one employed an interactive voice response system;[120] and one tested combinations of audiotapes and booklets.[124]

The remaining three trials focused on providers and systems in addition to patients.[125-127] Of these three, one trial evaluated shared and clinical decisionmaking between patients and clinicians,[127] and two evaluated changes in patient adherence when information delivery systems were altered to provide pharmacists[125] or physicians[126] with patient adherence information. The pharmacist trial provided patients in the two arms with peak flow monitors and pharmacists in all three arms with disease-specific training.[125]

Comparator

Six trials compared active arms to a control arm characterized as "usual care."[120-124,126] In two trials, usual care was minimally described;[120,121] in the remaining four trials, 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.[122-124,126] Data collection for control arms varied: e.g., minimal effort in one that relied on pharmacy refill data for outcomes[126] to fairly intense efforts in two that used daily monitoring of symptoms, medication use, and peak flow data during the intervention period.[122,123] Usual care varied in setting and intensity across the six trials.

Another trial 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.[127] The only trial without a usual-care arm involved a pharmacist intervention in which pharmacists in all arms received training.[125] 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

All trials reported on adherence. Seven of eight trials included percentage adherence as a measure, that is, number of doses taken relative to number prescribed. These trials 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 trial relied on self-reported measures of adherence alone.[125]

Among the trials that we evaluated for health and other outcomes, the primary morbidity measure was symptom severity or control, using self-reported measures. Trials used a wide range of measures and instruments; two trials used the same instrument (the Asthma Therapy Assessment Questionnaire).[124,127] One trial evaluated refills of short-acting beta-agonists (SABA) using refill data.[127]

The self-management interventions were generally short, 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 trial recorded 2- year adherence information for an intervention with an active component that lasted 9 months.[127] The two trials of system change recorded medication adherence at 1 year.[125,126]

Setting

Of the five self-management trials, four were conducted in one or more clinics[120,122-124] and another recruited directly from the community.[121] Interventions that focused on providers or the health system recruited local pharmacies in one case[125] and worked within health systems in the other two.[126,127]

Applicability

Two trials reported eligibility criteria in poor detail, making judgments about applicability challenging.[120,124] The remaining trials represent a broad range of severity overall, but the paucity of evidence for some types of interventions limits 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

- Eight trials provided evidence on medication adherence and other outcomes from interventions focusing on self-management, pharmacist or physician access to patient adherence information, and shared decisionmaking (Table 34).

Table 34. Reactive airway diseases: summary of findings

Type of Intervention	Study	Adherence: Measure, Followup Period Overall Result (+/=/-) and Timing	Additional Outcomes: Outcome Overall Result (+/=/-) and Timing
Self-management vs. usual care	Bender et al., 2010[120] N=50	+ Adherence rate, 10 weeks	= Symptoms, 10 weeks = Quality of life, 10 weeks
	Berg et al., 1997[121] N=55	+ Adherence rate, 7 weeks	= Symptoms, 7 weeks
	Janson et al., 2003[122] N=65	+ Adherence rate, 7 weeks	= Forced expiratory volume, 7 weeks = Symptom severity, 7 weeks + Perceived asthma control, 7 weeks = Quality of life, 7 weeks
	Janson et al., 2009[123] N=84	= Percentage adherence, 4 weeks and 14 weeks + Odds of maintaining >60% adherence, 4 weeks + Odds of maintaining >60% adherence, 14 weeks	= Forced expiratory volume, 4 weeks = Forced expiratory volume, 14 weeks = Frequency of nighttime awakenings, 4 weeks + Frequency of nighttime awakening, 14 weeks = Symptom-free days and symptom severity, 4 weeks and 14 weeks + Beta-agonist use, 4 weeks = Beta-agonist use, 14 weeks = Quality of life, 4 weeks and 14 weeks
	Schaffer et al., 2004[124] N=46	= Percentage adherence for all except one arm compared with control in a four-arm trial, 3 months + Percentage adherence for two of three arms compared with control in a four-arm trial, 6 months = Number of doses of preventive medication missed in previous 2 weeks, 3 and 6 months	= Asthma control, 3 months and 6 months = Quality of life, 3 months and 6 months
Pharmacist or physician access to patient adherence information vs. usual care or pharmacist training	Weinberger et al., 2002[125] N= 36 Pharmacies; 1,113 Patients	= Proportion of noncompliance = Self-reported compliance	NA
	Williams et al., 2010[126] N=207 Providers; 2,698 Patients	= Percentage adherence, 1 year	NA

Table 34. Reactive airway diseases: summary of findings (continued)

Type of Intervention	Study	Adherence: Measure, Followup Period Overall Result (+/=/-) and Timing	Additional Outcomes: Outcome Overall Result (+/=/-) and Timing
Shared decision-making vs. usual care	Wilson et al., 2010[127] N=612	+ Medication acquisition ratio for all drugs, 1 year and 2 years + Acquisition of inhaled corticosteroids, 1 year + Acquisition of beclomethasone, 1 year and 2 years + Acquisition of long-acting beta-agonists, 1 and 2 years	+ Forced expiratory volume, 1 year + Symptom improved: acquisition of short acting beta-agonists, 1 and 2 years + Asthma control, 1 year + Quality of life, 1 year + Health care utilization: asthma-related visits

Abbreviations: (+) = statistically significant difference favoring intervention arm(s); (=) = no statistically significant difference; (-) = statistically significant difference favoring comparison arm; N = number, NA = not applicable.

Self-Management

- Medication adherence: Adherence improved significantly during or immediately after the intervention was completed (five trials) (moderate strength of evidence for benefit); no information was available on longer-term effects (insufficient evidence).
- Biomarkers: Groups did not differ in pulmonary function and inflammation markers (insufficient evidence).
- Symptom improvement: Groups did not differ (insufficient evidence).
- Quality of life: Groups did not differ (four trials) (low strength of evidence of no benefit).

Pharmacist or Physician Access to Patient Adherence Information

- Medication adherence: Adherence did not improve significantly within the first year of initiating treatment (two trials) (low strength of evidence of no benefit).

Shared Decisionmaking

- Medication adherence: Adherence improved significantly within the first year of initiating treatment (one trial) (low strength of evidence of benefit).
- Biomarkers: Pulmonary function improved significantly within the first year of initiating treatment (low strength of evidence of benefit).
- Symptom improvement: Rescue medication use decreased significantly within 2 years of initiating treatment (low strength of evidence of benefit).
- Quality of life: Quality of life improved at 1-year assessment (low strength of evidence of benefit).
- Health care utilization: Asthma-related visits decreased within the first year of initiating treatment (low strength 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 percentage adherence in the intervention arm

compared with the control arm (Table 35).[120-122,124] In the remaining trial, percentage adherence did not differ significantly; however, 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).[123] Four of five trials limited measurement of outcomes to the end of the intervention period or a month thereafter.[120-123] The remaining trial found that the group receiving a combination of audiotape and booklet had significantly greater adherence than usual care at both 3 and 6 months[124]; the booklet group also had significantly higher adherence than usual care at 6 months. Other measures for this trial, 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 suggest improvement in adherence to various types of medications for this chronic disease during the intervention period (moderate strength of evidence for benefit). They offer only limited insight on whether improvements in adherence can be sustained over the long term (insufficient evidence) (Table 36).

Other Outcomes

We evaluated other outcomes for all five trials because all five reported at least one significant outcome relating to improved medication adherence (Table 36). Two asthma trials evaluated pulmonary function and some measures of inflammation through a variety of sputum markers (Appendix G).[122,123] Neither found differences between trial arms in pulmonary function (insufficient evidence); both reported significant improvement in one sputum marker each but acknowledged that the clinical role of these markers was unclear (insufficient evidence).

The five trials reported a wide variety of symptom improvement measures; two found no statistically significant improvements in the intervention arm compared with the control arm,[120,124] and one found a trend toward a higher percentage with symptom-free days in the control arm (insufficient evidence).[121] In the two trials 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 (insufficient evidence).[122,123]

Four trials evaluated quality of life and found no differences between trial arms (insufficient evidence) (Appendix G).[120,122-124]

Table 35. Asthma: medication adherence

Study	N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, direction)	Source	Baseline	First Followup	Additional Followups
Self-manage-ment	Bender et al., 2010[120] G1: 25 G2: 25	Adults ages 18 to 65 years Tertiary care center	G1: Interactive-voice-response phone calls to monitor symptoms and encourage adherence G2: Usual care (not described)	Two to three calls for 10 to 15 minutes, 10-week duration	Mean change in percentage adherence	Electronic metered devices	NR	4 weeks: G1: -0.18 G2: -1.40 95% CI, NR p=0.72	14 weeks: G1: -4.28 G2: -4.14 95% CI, NR p=0.97
	Berg et al., 1997[121] G1: 31 G2: 24	Adults >18 years Setting not specified, held in the community	G1: Sessions on asthma education, self-management behaviors, relaxation techniques, problem-solving skills G2: Usual care with physician	Six face-to-face visits, 7-week duration	Percentage adherence, 0 to 100% (SD)	Monitored inhaler and self-reported prescription information	G1: 43 (29) G2: 40 (26) 95% CI, NR p<0.05	7 weeks G1: 49 (31) G2: 32 (28) 95% CI, NR p<0.05	NR
	Janson et al., 2003[122] G1: 33 G2: 32	Adults ages 18 to 55 years 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	Five face-to-face visits, 7-week duration	Percentage adherence, 0 to 100% (SD)	Self-report, supplemented by medication monitors	G1: 70 (30) G2: 65 (34) p=NR	7 weeks: G1: 91 (32) G2: 62 (38) 95% CI, NR Between-group difference from baseline to 7 weeks, Mean (95% CI): 24 (5 to 43) p=0.01	NR

Table 35. Asthma: medication adherence (continued)

Study	N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Self-manage-ment (continued)	Janson et al., 2009[123] G1: 45 G2:39	Adults ages 18 to 55 years 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	Five face-to-face visits, 14-week duration	Percentage adherence, 0 to 100% (SD), Change in percentage adherence	Electronic metered devices	Percentage adherent G1: 82 (18) G2: 81 (18) p=0.71	Mean change in percentage at 4 weeks: G1: -0.18 G2: -1.40 95% CI, NR p=0.72	Mean change in percentage 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	NA	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[124] G1: 11 G2: 10 G3: 12 G4: 13	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	One contact, audio or book, duration NR	Proportion adherent (days of medication dispensed/ number of days between refill and date of study visit), (higher is better, 0 to 1)	Pharmacy refill data	Mean (SD): 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	Mean (SD): G1: 1.72 (2.15) G2: 8.10 (12.63) G3: 6.58 (9.52) G4: 3.61 (7.65)	NS for any group, 3 months	NS for any group, 6 months

Table 35. Asthma: medication adherence (continued)

Study	N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Physician or pharmacist access to patient data	Weinberger et al., 2002[125] G1: 356 G2: 296 G3: 246	Adults > 18 Pharmacy	G1: Pharmaceutical care program: Pharmacists given access to patient-specific data symptom, adherence, and health care utilization data; trained to access and interpret patient-specific information and educated about reactive airway disease; given incentives for high utilization of patient-specific data. Patients given peak-flow monitors, instructions about its use, and monthly calls to obtain PEFR results. G2: Peak-flow monitoring: pharmacists educated and patients given peak-flow monitors and monthly reminders to use peak-flow monitors. G3: Usual care: Pharmacists educated	>One face-to- face, print, duration NR	Proportion of noncom-pliance (higher is worse, 0 to 1)	Self-report	Percentage not compliant G1: 34.9 G2: 32.7 G3: 33.6	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)	NR
					Morisky scale, 0 (low) to 4 (high)	Self-report	Mean (SD) G1: 1.3 (1.2) G2: 1.2 (1.1) G3: 1.2 (1.2)	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	NR
	Williams et al., 2010[126] G1: 1335 G2: 1363	Primary care providers; Patients ages 5 to 56 years 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	>one computer, duration NR	Percentage adherence as a continuous measure of medication availability	Electronic prescription information and pharmacy claims data	Mean (SD) G1: 25.6 (37.3) G2: 27.7 (38.5) 95% CI, NR p=0.210	Mean at 12 months (SE): G1: 21.3 (2.5) G2: 23.3 (2.2) 95% CI, NR p=0.553	NR

Table 35. Asthma: medication adherence (continued)

Study	N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Shared decision-making or clinical decision-making	Wilson et al., 2010[127] G1: 204 G2: 204 G3: 204	Adults ages 18 to 70 years Kaiser Permanente medical centers	G1: Shared decisionmaking model G2: Clinical decisionmaking model G3: Usual care: Stepped approach to medications	Five face-to-face, phone, 9 months	Medication acquisition ratio for all asthma medications (total days supply acquired in a year/365 days)	Pharmacy refill data	NR	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 cortico-steroids (total days' supply acquired in a year/365 days)	Pharmacy refill data	NR	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	NR
					Acquisition of beclo-methasone canister equivalents	Pharmacy refill data	NR	Means at 1 year: 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 2 years: 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

Table 35. Asthma: medication adherence (continued)

Study	N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Shared decision-making or clinical decision-making (continued)					Medication acquisition for long-acting beta-agonists	Pharmacy refill data	NR	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; NA = not applicable; NR = not reported; OR = odds ratio; PEFR = peak expiratory flow rate; SD, standard deviation; SE, standard error.

Table 36. 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	Precise	Difference in percentage points for adherence: 14 to 31 (range) Moderate for benefit for duration of intervention Insufficient for longer-term effects
	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 for no benefit

Abbreviation: RCT = randomized controlled trial.

Detailed Synthesis: Interventions Providing Pharmacists or Physicians Access to Patient Adherence Data

Medication Adherence

Of three interventions aimed at providers and/or systems,[125-127] two focused on patient adherence when providers (pharmacists or physicians) were provided with patient adherence data (Table 35).[125,126] The pharmacist intervention, which provided additional elements of pharmacist care, examined the effects of this intervention separately for patients with asthma or COPD.[125] Neither trial found statistically significant differences between groups at 1 year following the start of the trial (low strength of evidence of no benefit) (Table 37).

Table 37. 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
Pharmacist or physician access to patient adherence data vs. usual care	2; 3,811 (3,596)	Medication adherence	RCT Low	Consistent	Direct	Precise	Difference of 2 percentage points in percent adherence; 0.5 to 0.7 difference in Morisky scale Low for no benefit

Abbreviation: RCT = randomized controlled trial.

Detailed Synthesis: Shared or Clinical Decisionmaking for Asthma

Medication Adherence

One trial compared either shared decisionmaking or clinical decisionmaking with usual care (Table 38). At 1 year, clinical decisionmaking was more effective than usual care and shared decisionmaking was more effective than either clinical decisionmaking or usual care (low strength of evidence for benefit).[127] 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 (low strength of evidence for benefit of shared decisionmaking).

Table 38. 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 or clinical 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 to 0.21 (range) Low for benefit
	1; 612 (551)	Pulmonary function	RCT Medium	Unknown	Direct	Precise	Difference in FEV1 percentage points: 2.7 to 3.4 Low for benefit
	1; 612 (612)	Symptom improvement	RCT Medium	Unknown	Direct	Precise	Difference in mean equivalents of SABA canister equivalents acquired at 2 years between shared decisionmaking and usual care: 1.6 Low for 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 for benefit
	1; 612 (612)	Health care utilization	RCT Medium	Unknown	Direct	Precise	Difference of 0.3 to 0.4 fewer asthma-related visits per year Low for benefit

Abbreviations: FEV1 = forced expiratory volume at 1 minute; NA = not applicable; RCT = randomized controlled trial; SABA = short-acting beta agonists.

Other Outcomes

This trial reported significantly improved pulmonary function for the shared decisionmaking group alone compared with usual care (Appendix G), suggesting evidence of benefit (Table 38).[127] At 1 year, both intervention groups had higher odds of reporting no asthma control problems than did the group receiving usual care, and both reported significantly lower acquisition of SABA compared with usual care (6.5 and 7.1 vs. 8.1 canister equivalents, $p>0.05$ [Appendix G]) (low strength of evidence for benefit). At 2 years, only the shared decisionmaking arm reported lower SABA use than usual care (4.7 vs. 6.3 canister equivalents, $p>0.05$). Both clinical and shared decisionmaking arms produced significantly higher quality of life and fewer asthma-related visits than usual care (Table 38).

Key Question 1. Depression: Medication Adherence Interventions

Description of Included Trials

Overview

We found 11 RCTs (reported in 14 articles) on depression[87,101,128-139] (Table 39). 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 trials for the detailed synthesis and then incorporated other dimensions of trial characteristics within these intervention clusters. We rated one trial as having low risk of bias[139] and all others as having medium risk of bias.

Table 39. Depression: summary of findings

Type of Intervention	Study	Adherence: Measure, Followup Period Overall Result (+/=/-) and Timing	Additional Outcomes: Outcome Overall Result (+/=/-) and Timing
Medication telemonitoring or telephone care	Rickles et al., 2005[128] N=63	= Antidepressant doses omitted over previous 3 months	NA
	Simon et al., 2006[129] N=207	= Filled prescriptions for at least 90 days over 6 months of continuous antidepressant treatment	NA
Case management	Bogner et al., 2007[101] N=64	+ Adherence for taking ≥80% antidepressant medications over 6 weeks	+ Depression severity, 6 weeks
	Bogner et al., 2010[87] N=58	+ Adherence for taking ≥80% antidepressant medications over 6 weeks	+ Depression severity, 6 weeks
	Katon et al., 2001;[130] Ludman et al., 2003;[131] Von Korff et al. 2003[132] N=386	+ Percentage who filled antidepressant prescriptions over 12 months + Percentage adherence over 12 months	+ Depression severity for patients with severe depression across 12 months = Self-reported functional impairment, 3, 6, 9, and 12 months
Collaborative care	Capoccia et al., 2004[133] N= 74	= Percentage adherent, 3, 6, 9, and 12 months	NA
	Katon et al., 1995[134] N=217	+ Adequate dosage of antidepressants for ≥30 days for patients with major or minor depression + Adequate dosage of antidepressants for ≥90 days for patients with major or minor depression	+ Depression severity for patients with major depression at 4 months = Depression severity for patients with minor depression at 4 months + Response to treatment for patients with major depression at 4 months = Response to treatment for patients with minor depression at 4 months + Patient satisfaction for patients with major or minor depression = Health care utilization + Patient satisfaction with quality of care

Table 39. Depression: summary of findings (continued)

Type of Intervention	Study	Adherence: Measure, Followup Period Overall Result (+/=/-) and Timing	Additional Outcomes: Outcome Overall Result (+/=/-) and Timing
Collaborative care (continued)	Katon et al., 1996[135] N=153	+ Adequate dosage of antidepressants for ≥30 days for patients with minor depression = Adequate dosage of antidepressants for ≥30 days for patients with major depression = Adequate dosage of antidepressants for ≥90 days for patients with major or minor depression + Percentage adherence for ≥25 of 30 days for major depression and minor depression for major and minor depression at 4 and 7 months	+ Response to treatment for patients with major depression at 4 months = Response to treatment for patients with minor depression at 4 months + Patient satisfaction for patients with major depression = Patient satisfaction for patients with minor depression = Health care utilization + Patient satisfaction with quality of care
	Katon et al., 1999;[136] Katon et al., 2002[137] N=228	+ Adequate dosage of antidepressants for ≥90 days in the past 6 months at 6 months for patients with moderate depression = Adequate dosage of antidepressants for ≥90 days in the past 6 months at 12, 18, 24, and 30 months for patients with severe depression + Adequate dosage of antidepressants for ≥90 days in the past 6 months at 6 and 12 months for patients with severe depression = Adequate dosage of antidepressants for ≥90 days in the past 6 months at 18, 24, and 30 months for patients with severe depression	+ Remission at 3 and 6 months + Depression severity for all patients at 3 and 6 months + Depression severity for patients with moderate severity over 28 months = Depression severity for patients with severe depression over 28 months = Functional impairment for patients with moderate and severe depression = Health care utilization = Costs + Patient satisfaction with quality of care
	Pyne et al., 2011[138] N=276	= Number with ≥ 80% adherence to antidepressants at 6 and 12 months	NA

Table 39. Depression: summary of findings (continued)

Type of Intervention	Study	Adherence: Measure, Followup Period Overall Result (+/=/-) and Timing	Additional Outcomes: Outcome Overall Result (+/=/-) and Timing
Reminders to nonadherent patients and lists of nonadherent patients to providers	Hoffman et al., 2003[139] N=9,564 patients; 7,021 providers	+ Percentage adherent (<10 gap days in a 30-day period), 3 and 6 months + Percentage adherence using HEDIS guidelines at 3 and 6 months = Persistence at 3 and 6 months	NR

Abbreviations: (+) = statistically significant difference favoring intervention arm(s); (=) = no statistically significant difference; (-) = statistically significant difference favoring comparison arm; HEDIS = Healthcare Effectiveness Data and Information Set; N = number; NA = not applicable; NR = not reported.

Population

One trial focused on patients with both depression and diabetes,[87] one on patients with depression and hypertension,[101] and one on patients with depression and HIV.[138] Eight trials did not specify that subjects had any chronic conditions other than depression.[128-137,139]

The 11 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.[128-133,136,137,139] 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.[130-132] Five trials did not require a new episode of depression as a condition of inclusion.[87,101,134,135,138] Two provided data separately for major and minor depression.[134,135] Another trial distinguished between moderate-severity and high-severity depression.[136,137]

Intervention

Of the 11 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;[128,129] 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.[128] 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.[129] This intervention was directed to patients with new episodes of depression, that is, no regular antidepressant use in the past 4 months.[128,129] 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 exception for

coexisting chronic disorder (diabetes in one case[87] and hypertension in the other[101]). 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.[87,101] A third trial, focusing on relapse prevention, was limited to patients with recurrent depression.[130-132]

Five trials focused on collaborative care models that required system-level changes.[133-138] 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. Four interventions included either specific courses of therapy[134,135] or stepped approaches to care and included in-person visits in the intervention arm.[136-138] 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.[133]

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.[139] 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; 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.[87,101,128,129] The collaborative care interventions used usual care as the comparator,[133-138] but usual care was specified as involving depression care by primary care physicians, including antidepressants and referrals to specialty mental health services when needed.[134-138]

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 persistence.[139] Medication adherence outcomes examined in the other trials included the following: whether the prescription was filled at successive time points;[130-132] dichotomous measures of adherence (taken vs. prescribed), using thresholds of 80 percent or higher[87,101,138] and 95 percent or higher;[138] 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);[136,137] dichotomous measures of gap days (e.g., less than 10 days over 30 days);[139] and continuous measures of doses omitted[128] over a given period of time. Two trials relied solely on self-reported measures of adherence;[133,138] all others used pharmacy refill or pharmacy claims data[128-132,134-137,139] or MEMS.[87,101] 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).[87,101] Three others used symptom improvement on the Hopkins Symptom Checklist (SCL-20);[130-132,134,136,137] 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.[134,136,137] One trial reported on health care utilization and costs.[134,136,137]

Most trials reported on outcomes during, immediately following, or within 3 months of the end of the intervention; intervention length ranged from 4 weeks[87,101] to 12 months.[130-133,138] 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.[133] Only one trial reported on long-term outcomes (up to 28 months after randomization); the active phase of this intervention lasted for a maximum of 3 months.[136,137] 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

Eight trials were set in primary care clinics: of these, two were in community-based primary care,[87,101] one was in university-based primary care clinics,[133] and five were in primary care clinics in one health care system (Group Health Cooperative).[129-132,134-137] Of the remaining trials, one was set in community pharmacies affiliated with a managed care organization;[128] one was in a Department of HIV clinic of the Department of Veterans Affairs (VA);[138] and one employed systems records within a large health maintenance organization.[139]

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 other teams can replicate their successes.

Key Points

Overview

- Eleven trials produced inconsistent evidence on medication adherence (Table 39).
- Five of 11 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 for benefit).
- Morbidity:
  - Case management improved symptoms of depression (moderate strength of evidence for benefit).
  - Case management had no statistically significant effect on self-reported disability (insufficient evidence).

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 (moderate strength of evidence for benefit).
  - Telephone-only collaborative care showed no statistically significant improvement in medication adherence (insufficient evidence).
  - No statistically significant difference in medication adherence was found for patients with depression and HIV (insufficient evidence).
- Morbidity:
  - Collaborative care reduced depressive symptoms in patients with major depression (low strength of evidence for benefit).
  - Collaborative care did not result in statistically significant improvement in depressive symptoms for patients with minor depression (insufficient evidence).
  - Collaborative care reduced depressive symptoms for patients with moderately severe depression (low strength of evidence for benefit).
- Patient satisfaction:
  - Collaborative care resulted in improved patient satisfaction with antidepressants (low strength of evidence for benefit).
- Health care utilization:
  - Evidence was insufficient for primary care or mental health visits.
  - Evidence was 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 for benefit)

Reminders to Nonadherent Patients and Lists of Nonadherent Patients to Providers

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

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 40).[128,129] The evidence is insufficient for the effects of telephone-only interventions with low intensity and short duration for medication adherence (Table 41).

Table 40. Depression: medication adherence

Type of Intervention	Study N per Group	Sample and Setting	Intervention Groups	Intervention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Medication telemonitoring or telephone care	Rickles et al., 2005[128] G1: 28 G2: 32	Patients ≥18 years Pharmacies	G1: Pharmacists called patients 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	Three phone contact over 3 months	Antidepressant doses omitted over previous 3 months	Pharmacy refill	NR	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[129] G1: 98 G2: 97	Patients ≥18 years Phone contacts	G1: Contacts 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	Three phone contact over 3 months	Filled prescriptions for at least 90 days over 6 months of continuous antidepressant treatment	Pharmacy refill	NR	At 6 months: G1: 63 (64%) G2: 53 (55%) 95% CI, NR Chi-square (1 df): 1.88 p=0.17	NR
Case management	Bogner et al., 2008[101] G1: 32 G2: 32	Adults ≥50 years with depression and HTN Primary care clinic	G1: Integrated care of depression and hypertension with care manager G2: Usual care	Three face-to-face + two calls over 4 weeks	Number of patients with ≥80% adherence to depression medications (0 to 100%)	MEMS	G1: 16 (50.0%) G2: 14 (43.0%) 95% CI: NR p: 0.81	6 weeks: G1: 23 (71.9%) G2: 10 (31.3%) 95% CI, NR p=0.001	NR

Table 40. Depression: medication adherence (continued)

Type of Intervention	Study N per Group	Sample and Setting	Intervention Groups	Intervention Dose	Measure (Range, direction)	Source	Baseline	First Followup	Additional Followups
Case management (continued)	Bogner et al., 2010[87] G1: 29 G2: 29	Adults ≥50 years 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	Three face-to-face + two calls over 4 weeks	Number of patients with ≥80% adherence to depression medications (0 to 100%)	MEMS	G1: 8 (27.6%) G2: 4 (13.8%) 95% CI: NR p: 0.17	**6 weeks**: G1: 18 (62.1%) G2: 3 (10.3%) 95% CI, NR p<0.001	NR
	Katon et al., 2001;[130] Ludman et al., 2003;[131] Von Korff et al. 2003[132] G1: 170 G2: 145	Patients 18 to 80 years Primary care clinics	G1: Depression relapse prevention program including education, symptom monitoring, motivational enhancement, self-management and self-care instruction, and referral facilitation G2: Usual care: two to four visits in first 6 months following antidepressant prescription; referral to mental health services as needed.	Nine face-to-face, phone, print, DVD contact over 12 months	Percentage who filled antidepressant prescriptions	Pharmacy refill data	NR	0 to 3 months (95 % CI): G1: 80.7 % (75.1 to 86.3) G2: 65.6 % (58.8 to 72.4)	3 to 6 months (95 % CI): G1: 71.9 % (65.5 to 78.2) G2: 58.2% (51.2 to 65.2) 6 to 9 months (95 % CI): G1: 68.4% (61.8 to 75.0) G2: 55.6% (48.5 to 62.7) 9 to 12 months (95 % CI): 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

Table 40. Depression: medication adherence (continued)

Type of Intervention	Study N per Group	Sample and Setting	Intervention Groups	Intervention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Case management (continued					Adequate dose of antidepressant medication	Pharmacy refill data	NR	NR	Adjusted odds ratio (95% CI) across 12 months: 2.08 (1.41 to 3.06) p<0.001
Collaborative care	Capoccia et al., 2004[133] G1: 41 G2: 33	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 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	18 phone contact over 12 months	Adherent to antidepressants (taken ≥25 days of previous 30 days)	Question-naire	NR	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

Table 40. Depression: medication adherence (continued)

Type of Intervention	Study N per Group	Sample and Setting	Intervention Groups	Intervention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Collaborative care (continued)	Katon et al., 1995[134] Major depression: 91 G1: 49 G2: 42 Minor depression: 126 G1: 59 G2: 67	Patients 18 to 80 years Primary care clinics	G1: Patients received education on depression, antidepressants, and CBT management techniques; completed a doctor-patient questionnaire to give 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	Four face-to-face, print, video contact over 6 weeks	Patients receiving adequate dosage of antidepressants in continuation phase (3 to 7 months) for ≥30 days	Pharmacy refill data	NR	Percentage from 3 to 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	NR
					Patients receiving adequate dosage of antidepressants in continuation phase (3 to 7 months) for ≥90 days	Pharmacy refill data	NR	Percentage from 3 to 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	NR

Table 40. Depression: medication adherence (continued)

Type of Intervention	Study N per Group	Sample and Setting	Intervention Groups	Intervention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Collaborative care (continued)	Katon et al., 1996[135] Overall G1: 77 G2: 76 Major depression: 65 G1: 31 G2: 34 Minor depression: 88 G1: 46 G2: 42	Patients 18 to 80 years 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.	Eight face-to-face, print, phone, video, over 24 weeks	Patients receiving adequate dosage of antidepressant medication for ≥30 days (AHCPR guidelines)	Pharmacy refill data	NR	Timeframe unspecified 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	NR
					Patients receiving adequate dosage of antidepressant medication for ≥90 days (AHCPR guidelines)	Pharmacy refill data	NR	Timeframe unspecified 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	NR

Table 40. Depression: medication adherence (continued)

Type of Intervention	Study N per Group	Sample and Setting	Intervention Groups	Intervention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Collaborative care (continued)					Percentage adherent to antidepressants (taken ≥25 days of previous 30 days)	Questionnaire	NR	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	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 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

Table 40. Depression: medication adherence (continued)

Type of Intervention	Study N per Group	Sample and Setting	Intervention Groups	Intervention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Collaborative care (continued)	Katon et al., 1999;[136] Katon et al., 2002[137] G1: 114 G2: 114	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.	>Two face-to-face, phone, print, DVD over NS period	Percentage of patients receiving adequate dosage of anti-depressants for ≥ 90 days in previous 6 months (per AHCPR guideline)	Pharmacy refill data	NR	Percentage: G1: 68.8% G2: 43.8% 95% CI, NR Chi-square (1 df): 12.60 p=0.0001	NR
					Patients receiving twice the dosage of the lower range (per AHCPR guideline)	Pharmacy refill data	NR	Timeframe NR Percentage: G1: 46.8% G2: 25.7% 95% CI, NR Chi-square (1 df): 9.36 p=0.002	NR
					Adherent to anti-depressants (taken ≥25 days of previous 30 days)	Questionnaire	NR	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 40. Depression: medication adherence (continued)

Type of Intervention	Study N per Group	Sample and Setting	Intervention Groups	Intervention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Collaborative care (continued)			Among patients with moderate depression (defined as SCL-20 score ≤2.0 at baseline) N=149		Patients receiving adequate dosage of anti-depressants for at least 90 days out of previous 6 months	Pharmacy refill data	NR	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 anti-depressants for at least 90 days out of previous 6 months	Pharmacy refill data	NR	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

Table 40. Depression: medication adherence (continued)

Type of Inter-vention	Study N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Collabo-rative care (continued)	Pyne et al., 2011[138] G1: 123 G2: 126	Patients with HIV infection 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	>1 phone contact for patients, NR for provider	Number of patients with ≥80% adherence to depression medications (0 to 100%)	Question-naire	Mean percentage (SD) G1: 85.4 (30.5) G2: 86.4 (31.1)	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

Table 40. Depression: medication adherence (continued)

Type of Intervention	Study N per Group	Sample and Setting	Intervention Groups	Intervention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Reminders to nonadherent patients and lists of nonadherent patients to providers	Hoffman et al., 2003[139] G1: 4899 Pts. G2: 4665 Pts.	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	Six print and mail contact over 6 months	Percentage adherent to antidepressants (<10 gap days in a 30-day period)	Pharmacy claims records	NR	Percentage adherent at 1 month: G1: 58.9% G2: 57.4% 95% CI, NR p=0.136	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	Pharmacy claims records	NR	Percentage adherent at 3 months (a total of 30 gap days in days 1 to 84 of treatment): G1: 59.6% G2: 56.6% 95% CI, NR p<0.01	Percentage adherent at 6 months (a total of 51 gap days in days 1 to 180 of treatment): G1: 31.5% G2: 29.4% 95% CI, NR p<0.05

Table 40. Depression: medication adherence (continued)

Type of Intervention	Study N per Group	Sample and Setting	Intervention Groups	Intervention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Reminders to nonadherent patients and lists of nonadherent patients to providers (continued)					Persistency (patient considered persistent if date of the last prescription filled plus the days' supply was ≤10 days from the end of the trial)	Pharmacy claims records	NR	Mean percentage at 2 months: G1: 45.9% G2: 44.3%	Mean percentage (SD) from 1 to 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 to 180 days: G1: 24.9%(51.9) G2: 23.3%(51.9) Chi-square (1 df): 0.067 95% CI, NR p:NR

Abbreviations: ACE = angiotensin-converting enzyme; AHCPR = Agency for Health Care Policy and Research; CBT = cognitive behavioral therapy; CI = confidence interval; df = degrees of freedom; DVD = digital video disk; G = group; HEDIS = Healthcare Effectiveness Data and Information Set; ITT = intention to treat; MEMS = medication event monitoring systems; N = number; NR = not reported; NS = not statistically significant; PCP = primary care provider; RCT = randomized controlled trial; SCL-20 = Hopkins Symptom Checklist-20; SD = standard deviation; VA = Department of Veterans Affairs.

Table 41. 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	No statistically significant difference Insufficient

Abbreviation: RCT = randomized controlled trial.

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 40).[87,101,130-132] 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 42). No evidence is available to evaluate the utility of this intervention for improving medication adherence over the longer term (after completion of the intervention).

Table 42. 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 to 15 (range across studies) Moderate
	3; 508 (437)	Symptom improvement	RCT Medium	Consistent	Direct	Precise	Difference in CES-D scale: 7.0 to 9.4 (range across studies) Mean difference in SCL-20 (0 to 4 range) scores between groups across 12 months: 0.08 Moderate
	1; 386 (315)	Self-reported disability	RCT Medium	Unknown	Indirect	Imprecise	Varied measures, outcomes, time periods Insufficient

Abbreviations: CES-D scale = Center for Epidemiologic Studies-Depression scale; RCT = randomized controlled trials; SCL-20 = Hopkins Symptom Checklist-20; vs. = versus.

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,[87,101] and the 12-month intervention reported outcomes at 3, 6, 9, and 12 months.[51-53] All three trials demonstrated significant differences at followup favoring the intervention arm over the control arm for symptoms of depression (moderate strength of evidence of benefit) (Table 42).[87,101,130-132] One trial, on relapse prevention, 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.[130-132] Only the SF-36 Social Functioning scale measure demonstrated a significant difference between intervention and control arm.[130-132] This evidence is insufficient to draw conclusions about the effectiveness of case management to improve self-reported disability outcomes (Table 42). The trials did not report mortality, patient satisfaction, health care utilization, or costs.

Detailed Synthesis: Collaborative Care Interventions for Depression

Medication Adherence

The five collaborative care interventions varied by population and components.

Three other collaborative care interventions were developed and implemented by investigators common to all three trials and carried out in similar settings. They differed in structure (stepped care with the number of contacts and course of treatment tailored to the patient[136,137] vs. a common protocol for all patients[134,135]) and in process (alternate visits to psychiatrists and primary care[134] vs.psychiatrists[136,137] or psychologists[135] serving as central agent of delivery of the intervention). Two of these trials were stratified by major and minor depression;[134,135] a third selected patients for persistence (based on SCL-20 scores) and then stratified by severity of depression;[136,137] in addition, one trial presented results for the overall group.[136]

Of the two trials that stratified subjects 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.[134] The other trial found improved medication adherence (percentage adherent) in the intervention arm compared with the control arm at 4 and 7 months after randomization for both major and minor depression patients; with the exception of the 7-month followup for major depression, these differences were statistically significant at $p<0.05$.[135] The trial did not demonstrate significant difference for measures of adequacy of prescription for either major or minor depressive groups.

One trial continued to record medication adherence outcomes for 6-month intervals through 30 months after randomization;[136,137] it reported overall differences by intervention arms at 3 and 6 months after randomization.[136,137] Among patients severely depressed at baseline, the intervention arm continued to show benefits of the intervention on medication adherence at 12 months.[136,137] 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 that collaborative care interventions produced improvements in medication adherence overall (moderate strength of evidence of benefit) (Table 43).

Of the two other trials, one focused on providing populations with interventions for depression and HIV infection.[138] It 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.[138] This trial showed no statistically significant effect of the intervention arm on medication adherence.

A second 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."[133] Their interaction with patients was limited to (a) weekly telephone calls in the first 4 weeks, (b) biweekly calls through week 12, and (c) 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 two interventions is insufficient to judge their effectiveness (Table 43).

Other Outcomes

All three collaborative care interventions that showed a difference between arms for medication adherence reported on changes in depression symptoms (Appendix G). Two demonstrated statistically significant improvements in response (difference in response to treatment varied from 28.1 to 30.6 percentage points, $p<0.05$) and in symptoms using the SCL-20 scale in the group with major depression but not in the group with minor depression (difference in response to treatment varied from 7.9 to 13.9 percentage points, $p>0.2$).[134,135] A third trial, with stratified results for patients with moderate or severe depression, found statistically significant differences in depression severity at 28 months following randomization in the intervention arm compared with usual care for patients with moderate depression (0.88 vs. 10.23 on a 0-4 SCL-20 depression score, $p=0.004$) but not for those with severe depression (1.16 vs. 1.19, $p=0.88$).[136,137] Table 43 provides strength-of-evidence grades for this limited body of trials that suggest benefit from collaborative care (low strength of evidence).

Two trials reported improvement in patients' viewing antidepressant therapy as helping somewhat to a great deal (21.7 to 24.8 percentage points difference for major depression, 6.0 to 20.4 percentage points difference for minor depression) (low strength of evidence).[134,135] Three trials reported on health care utilization and found conflicting but nonsignificant differences between arms (insufficient evidence).[134-137] One trial examined costs and found no difference between trial arms (insufficient evidence).[136,137] All three trials found greater patient satisfaction with quality of care in the intervention arm than in usual care (moderate strength of evidence).[134-137] This difference was not statistically significant for the patient group with minor depression in one trial;[134] for the remaining trials and groups, the difference in percentage points for patients rating the quality of care received for depression as good to excellent ranged from 16 to 32.5.

Table 43. 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
	1; 249 (249) Depression and HIV	Medication adherence	RCT Medium	Unknown	Direct	Imprecise	Difference in percentage points for adherence: -8.7 to 9.4 (range) Insufficient for patients with depression and HIV
	1 (telephone only); 74 (74)	Medication adherence	RCT Medium	Unknown	Direct	Imprecise	Difference in percentage points for adherence: -19 to 2 (range across study) Insufficient
	2; 156 (156) Major depression	Symptom improvement	RCT Medium	Consistent	Direct	Precise	Varied magnitude based on outcome and time periods Low
	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
	1; 79 (79) Severe depression	Symptom improvement	RCT Medium	Unknown	Direct	Imprecise	Varied magnitude based on outcome and time periods Insufficient
	2; 370 (370)	Patient satisfaction with utility of antidepres-sants	RCT Medium	Consistent	Direct	Imprecise	Difference in percentage points in those rating antidepressants as helping somewhat to a great deal: 6.0 to 24.8 (range across studies) at 4 months Low
	3; 598 (598)	Health care utilization	RCT Medium	Inconsistent	Direct	Imprecise	Varied outcomes, time periods, and consistency Insufficient

Table 43. 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
Collaborative care vs. usual care (continued)	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 to 32.5 (range across studies) at 3 to 4 months; 16 at 6 months Moderate SOE

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

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.[139] Patients in the intervention arm had significantly higher medication adherence at 3 and 6 months than those in the control arm of usual care (Table 40). Depending on the measure used (10 gap days or MPR) and the time span for the outcome (1 month, 90 days, 180 days), the difference between the arms ranged from 1 to 3 percentage points (low strength of evidence) (Table 44).

Table 44. Depression: strength of evidence for reminders to providers and nonadherent patients interventions

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Study Design/Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Reminders vs. usual care	1; 9,564 (9,564)	Medication adherence	RCT Medium	Consistent	Direct	Precise	Difference in percentage points for adherence; 1 to 3 (range across study) Low

Abbreviation: RCT = randomized controlled trials.

Other Outcomes

The authors of this trial noted the unknown clinical significance of such a difference in adherence rates but they offered no additional data to evaluate the effect of the intervention on health outcomes.

Key Question 1. Glaucoma: Medication Adherence Interventions

Description of Included Studies

Overview

One trial, rated medium for risk of bias, examined an intervention that attempted to improve medication adherence among patients with glaucoma.[140]

Population

The trial 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 trial was directed at patients. It tested a multicomponent intervention consisting of an education video, discussion of barriers and strategies, reminder telephone 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 trial did not report on the initiation of therapy; it 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 initial 3-month observational cohort period and the end of the RCT period in the trial, 6 months into the overall trial period). These measurements were taken using a dosing aid that was downloaded at the appropriate times for measurement. This trial reported a significantly higher medication adherence in the intervention arm than in the control arm. The trial reported a health outcome of intraocular pressure for glaucoma patients measured in millimeters of mercury (mm Hg).

Setting

The trial was conducted at two eye clinics.

Applicability

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

Key Points

Overview

- A single trial provided evidence on improving medication adherence and other outcomes for glaucoma (Table 45).

Table 45. Glaucoma: summary of findings

Type of Intervention	Study	Adherence: Measure, Followup Period Overall Result (+/=/-) and Timing	Additional Outcomes: Outcome Overall Result (+/=/-) and Timing
Multicomponent intervention including an educational video, discussion of barriers, reminder calls, and dosing aid	Okeke et al., 2009[140] N=127	Adherence rate, 3 months after intervention Change in adherence rate (unadjusted), change between 3 and 6 months Change in adherence rate (adjusted), change between 3 and 6 months	Intraocular pressure, change between 3 and 6 months

Abbreviations: (+) = statistically significant difference favoring intervention arm(s); (=) = no statistically significant difference; (-) = statistically significant difference favoring comparison arm; N = number

Multicomponent Intervention for Glaucoma

- Medication adherence: One trial provided evidence of 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 (insufficient).

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) (low strength of evidence for benefit) (Table 46).

This trial 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 47).

Table 46. Glaucoma: detailed medication outcomes

Type of Intervention	Study N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Multicomponent	Okeke et al., 2009[140] G1: 35 G2: 31	Adults with glaucoma, glaucoma suspect, open-angle glaucoma, angle-closure glaucoma, or ocular hypertension Two eye clinics	G1: Educational video, discussion of barriers and strategies with study coordinator, reminder phone calls,, use of a dosing aid G2: Controls were told that it is important to take their eye drops as prescribed, but had no other intervention	10-minute educational video; reminder call once a week for first followup month and every other week for the next 2 months	Adherence rate	Dosing aids	3 months before intervention Adherence rate: G1: 0.54 (0.17) G2: 0.46% (0.23) P = 0.10	3 months after intervention: G1: 0.73 (0.22) G2: 0.51 (0.30) 95% CI, NR P= 0.001	Change between 3 and 6 months (unadjusted): G1: 0.19 (0.20) G2: 0.06 (0.23) 95% CI, NR P = 0.01 Change between 3 and 6 months (adjusted): G1: 0.21 (0.05) G2: -0.002 (0.04) 95% CI, NR P= 0.0001

Table 47. 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
Multi-component vs. usual care	1; 66 (66)	Proportion of prescribed doses taken	RCT Medium	Unknown	Direct	Precise	Difference in adherence rate: 0.22 Low
	1; 66 (66)	Morbidity: Intraocular pressure	RCT Medium	Unknown	Direct	Imprecise	Insufficient

Abbreviations: N=number; RCT=randomized controlled trial.

Key Question 1. Multiple Sclerosis: Medication Adherence Interventions

Description of Included Studies

Overview

One trial, with medium risk of bias, provided evidence on a software-based telephone counseling intervention to improve medication persistence among patients with multiple sclerosis (MS).[141]

Population

The trial population consisted of adult patients who were on Avonex® (interferon beta-1a) treatment for their MS (Biogen Idec manufactures Avonex, the MS treatment examined in this trial).

Software-Based Telephone Counseling Intervention

The intervention was directed at patients and systems. In this trial, call center staff at the Biogen call center 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 they were provided with a toll-free hotline number with which they could reach the call center if needed.

Outcome and Timing

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

Setting

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

Applicability

Although the intervention itself was broadly applicable among MS patients, recruitment of patients was stratified by stage of readiness to discontinue Avonex treatment. The recruitment process involved contacting sufficient participants to get adequate representation across all three stages, which likely makes the study population not representative of the overall MS patient population and hence limits applicability of findings.

Key Points

Overview

- A single trial intervention, which used software to guide telephone counselors through their conversations with MS patients, significantly improved medication persistence for patients with MS (Table 48).

Table 48. Multiple sclerosis: summary of findings

Type of Intervention	Study	Adherence: Measure, Followup Period Overall Result (+/=/-) and Timing	Additional Outcomes: Outcome Overall Result (+/=/-) and Timing
Counseling (software-based telephone) vs. usual care	Berger et al., 2005 [141] N=435	+ Percentage of patients who discontinued use of Avonex therapy for multiple sclerosis	NR

Abbreviations: (+) = statistically significant difference favoring intervention arm(s); (=) = no statistically significant difference; (-) = statistically significant difference favoring comparison arm; N = number; NR = not reported.

Software-Based Telephone Counseling Intervention for MS

- Medication persistence: The software-based telephone intervention reduced the percentage of patients who discontinued use of the MS medication (low strength of evidence for benefit).

Detailed Synthesis of Results

The intervention, based on the transtheoretical model of change, significantly improved medication persistence for individuals with MS (Table 49, as measured by proportion of patients who discontinued MS treatment) when compared with those who did not receive this intervention (low strength of evidence for benefit) (Table 50).

Table 49. Multiple sclerosis: detailed medication outcomes

Type of Interven-tion	Study N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, direction)	Source	Base-line	First Followup	Additional Followups
Counseling (software-based telephone)	Berger et al., 2005 [141] G1: 172 G2: 195	Adults currently on MS therapy with Avonex Network of patients with MS contacted by Biogen (manufac-turer of this drug)	G1: Software-based counseling intervention to contact patients (depending on stage of readiness and importance of continuing the medicine); call center staff used Web-based software to guide them through motivational interviewing based counseling sessions. G2: Patients did not receive calls, but had access to call center staff via standard toll-free hotline mechanisms.	Every 2 or 4 weeks	Percentage of patients who discontinued use of Avonex therapy for MS	Self-report	NR	G1: 2 (1.2%) discontinued G2: 17 (8.7%) discontinued 95% CI, NR P= 0.001	NR

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

Table 50. Software-based telephone counseling interventions for multiple sclerosis: strength of evidence

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Counseling (software-based telephone) vs. less intense intervention	1; 435(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

Abbreviations: MS = multiple sclerosis; N = number; RCT = randomized controlled trial.

Key Question 1. Musculoskeletal Diseases: Medication Adherence Interventions

Description of Included Studies

Overview

Three trials examined interventions designed to improve medication adherence in populations that had musculoskeletal diseases.[142,143] We rated two trials as having low risk of bias[142,144] and the other as having medium risk of bias.[143]

Population

One trial focused on populations with rheumatoid arthritis, psoriatic arthritis, and inflammatory arthritis.[142] The other two trials focused on populations with osteoporosis or osteopenia.[143,144]

Intervention

Two trials were directed at patients and systems-level change.[142,143] In one, the intervention consisted of case management, 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.[142] In the other trial, the intervention group received care from a physician assistant and monthly telephone conversations with staff in a virtual osteoporosis clinic. One trial, directed only at patients, involved use of a decision aid (a tailored pictographic 10-year fracture risk estimate, absolute risk reduction with bisphosphonates, side-effects, and out-of-pocket cost).[144]

Comparator

In one trial, patients in the control group received standard care, defined as care from their rheumatologist;[142]In addition, they received pamphlets from the Arthritis Foundation, examples of medicine calendars, and a map of the hospital (but not educational visits).[142] In another trial, the control group received usual care, defined as referral to and evaluation and treatment from, a primary care physician.[143] Finally, in a third, the control group received usual care, defined as

review of bone mineral density results without calculations of fracture risk in addition to a standard brochure.[144]

Outcome and Timing

One trial examined adherence.[142] 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).[142] The change in adherence from baseline to various time points was measured.[142] Another trial examined initiation of treatment measured by examining the percentage of study subjects who filled osteoporosis medication within 130 days of enrolling in the trial.[143] In addition, for those trials in which medication adherence improved significantly, 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 trial.[143] The third trial, which focused only on patients, assessed adherence, persistence, and initiation of therapy.[144] Adherence and persistence were measured at 6 months using pharmacy refill data;[144] adherence was measured at 6 months by self-report.[144] Initiation of bisphosphonates therapy was measured at baseline using pharmacy refill data.[144]

Setting

One trial was conducted in an arthritis center of an urban teaching hospital.[142] Another focused on patients with osteoporosis, was conducted at the Kaiser Permanente San Diego Department of Preventive Medicine.[143] The third trial, focused on patients with osteoporosis or osteopenia, was conducted in 10 general medicine and primary care practices that were affiliated with the Mayo Clinic in Minnesota.[144]

Applicability

We found all three trials to be broadly applicable to patients with these conditions because of the potential ease with which the interventions described could be more broadly applied and the types of primary care settings in which they were conducted.[142-144]

Key Points

- Three trials evaluated medication adherence. Two reported significant improvement in medication adherence but, in one, improvement in medication adherence was seen only in one of the adherence outcomes reported (Table 51).
- Two trials were directed at patients and systems-level change; one was directed only at patients.
- We evaluated other outcomes (patient satisfaction) for the two trials that showed improvement in medication adherence (insufficient evidence).
- We graded strength of evidence formally for the three trials separately, which equated to grading the following three kinds of interventions: (1) case management, (2) virtual clinic, and (3) a decision aid. We judged the body of evidence as low for the virtual clinic and insufficient evidence for case management and decision aid interventions due to lack of precision.

Table 51. Musculoskeletal diseases: summary of findings

Type of Intervention	Study	Adherence: Measure, Followup Period Overall Result (+/=/-) and Timing	Additional Outcomes: Outcome Overall Result (+/=/-) and Timing
Case management	Rudd et al., 2009[142]	= Mean score on adherence to treatments scale (0=best, 3=worst) = Percentage change at 6 months in medication adherence outcome = Percentage change at 12 months in medication adherence outcome	NA
Virtual osteoporosis clinic	Waalen et al., 2009[143]	+ Percentage of women using osteoporosis medication, at 13 months from entry into study	= Patient satisfaction with care, at 1 year and 30 days from entry into study
Decision aid	Montori et al., 2011[144]	+ Proportion with > 80% adherence, 6 months = Proportion of days covered, 6 months = Persistence, 6 months = Proportion that did not miss a dose, 6 months = Started therapy, baseline	= Mean satisfaction with knowledge transfer

Abbreviations: (+) = statistically significant difference favoring intervention arm(s); (=) = no statistically significant difference; (-) = statistically significant difference favoring comparison arm; N = number.

Detailed Synthesis for Interventions for Musculoskeletal Diseases

Medication Adherence

One trial 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 52 and Table 53, low strength of evidence of benefit).[143] In this trial, 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.

Another trial, using a decision aid as the intervention, measured initiation of therapy at baseline using pharmacy refill data (Table 52).[144]

One trial, using a case management intervention, examined adherence but did not show a significant effect of the intervention on adherence (Table 52).[142]

The trial using the decision aid examined adherence and showed a significant difference in the proportion of patients with more than 80 percent adherence at 6 months among those in the intervention group, as compared with the control group. Other medication adherence outcomes in the same trial showed no significant differences between the intervention and the control. The same trial measured initiation of therapy at baseline.[144] This trial also examined persistence in adherence and did not show significant difference of the intervention.[144]

We judged the body of evidence as insufficient to rate strength of evidence for the case management and decision aid interventions (Table 54 and Table 55).

Table 52. Musculoskeletal conditions: detailed medication outcomes

Type of Intervention	Study N per Group	Sample and Setting	Intervention Groups	Intervention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Case management	Rudd et al., 2009[142] Adherence baseline G1: 51 G2: 63 Adherence 6 months G1: 49 G2: 57 Adherence 12 months G1: 48 G2: 57 Percentage change 6 months G1: 49 G2: 57 Percentage change 12 months G1: 48 G2: 57	Adults with arthritis; who had ≥one visit with rheumatologist Arthritis center in urban teaching hospital	G1: Case management that included standard rheumatology care; a notebook containing Arthritis Foundation pamphlets written in plain language, examples of medicine calendars, and hospital map; two appointments with health educator. G2: Standard rheumatology care and a notebook containing Arthritis Foundation pamphlets, examples of medicine calendars, and hospital map.	Individualized care involved two appointments, 1 hour each, with an educator	Mean score on adherence to treatments scale (0=best, 3=worst)	Self-report	G1: 0.40 (0.40) G2: 0.30 (0.37)	6 months: 6-month mean (SD) G1: 0.23 (0.28) G2: 0.24 (0.32)	12 months: 12-month mean (SD) G1: 0.17 (0.25) G2: 0.18 (0.30)
					Percentage change medication adherence outcome	Self-report		6 months G1: -4.76 G2: 0.25 95% CI, NR p= 0.33	12 months G1: -12.21 G2: -3.12 95% CI, NR p= 0.10

Table 52. Musculoskeletal conditions: detailed medication outcomes (continued)

Type of Inter-vention	Study N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Virtual osteo-porosis clinic	Waalen et al., 2009 [143] G1: 109 G2: 102	Women ≥60 years, who had uncomplicated osteoporosis 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 physician. G2: Patients received a referral to their usual primary care physician and were told they would be contacted by the PCP for followup. No further contact with the patient was initiated by the osteoporosis clinic until the end of the study.	One-time mailing; open-ended telephone conversa-tion	Percentage of women using osteoporosis medication Measured at 1 year and 30 days from entry into study	Pharmacy database	NR	G1: 68.8% G2: 45.1% 95% CI, NR p: <0.001	NR
Decision aid	Montori et al., 2011[144] Initiation: Started therapy G1 52 G2: 48 Adherence: > 80% days covered: G1: 23 G2: 19 Adherence: Median (range) proportion of days covered: G1: 23 G2: 19	Postmenopausal women, ≥50 years, bone mineral density levels consistent with osteopenia or osteoporosis, not already under osteoporosis medication, found eligible for bisphosphonate therapy, had a followup appointment with clinician and were available for phone followup 6 months from initial appointment	G1: Intervention patients received a decision aid in addition to usual care. G2: Control patients received a standard brochure in addition to usual care.	Patients in intervention group had access to the decision aid during their consultation with a physician, discussed the decision aid during the consultation, and then took the decision aid home.	Initiation: Started therapy	Pharmacy refill data	Total G1: 44% G2: 40% 95% CI: NR p= NR <10% Risk Category G1: 50% G2: 25% 95% CI: NR p= NR 10 to 30% Risk Category G1: 45% G2: 45% 95% CI: NR p= NR	NA	NA

Table 52. Musculoskeletal conditions: detailed medication outcomes (continued)

Type of Intervention	Study N per Group	Sample and Setting	Intervention Groups	Intervention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Decision aid (continued)	Persistence: Median (range) number of days covered G1: 23 G2: 19 Adherence: Did not miss a dose G1: 17 G2: 19	10 general medicine and primary care practice in MN, affiliated with the Mayo Clinic					>30% Risk Category G1: 40% G2: 33% 95% CI: NR p=NR		
					Adherence: > 80% days covered	Pharmacy refill data	NR	6 months G1: 100% G2: 74% 95% CI: NR p=0.009	NR
					Adherence: Median (range) proportion of days covered	Pharmacy refill data	NR	6 months G1: 100 (86.1 to 100) G2: 98.2 (0 to 100) 95% CI: NR p= 0.09	NR
					Persistence: Median (range) number of days covered	Pharmacy refill data	NR	6 months G1: 170 (30 to 180) G2: 180 (28 to 180) 95% CI: NR p= 0.38	NR
					Adherence: did not miss a dose	Self-report	NR	6 months G1: 65% G2: 63% 95% CI: NR p=0.92	NR

Abbreviations: CI = confidence interval; G = group; NR = not reported; PA = Physician Assistant.

Table 53. Virtual clinic interventions for musculoskeletal diseases: strength of evidence

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Virtual clinic vs. usual care	1; 235 (211)	Initiation of treatment	RCT Medium	Unknown	Indirect	Precise	Difference in percentage of women using osteoporosis medication at (G1 vs. G2) at 13 months: 23.7 Low
	1; 235 (211)	Patient satisfaction	RCT Medium	Unknown	Direct	Imprecise	No statistically significant difference Insufficient

Abbreviations: G = group; RCT = randomized controlled trial; vs. = versus.

Table 54. Case management interventions for musculoskeletal diseases: strength of evidence

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Case management vs. usual care	1; 127 (127)	Medication adherence	RCT Low	Unknown	Direct	Imprecise	Difference in mean adherence score (G1 vs. G2) at 6 months: -0.01 Insufficient

Abbreviations: G = group; RCT = randomized controlled trial; vs. = versus.

Other Outcomes

In one trial where medication adherence outcomes were improved for those in the intervention group,[143] patient satisfaction outcomes were collected using a poststudy questionnaire completed by approximately 65 percent of women in both the intervention and the control groups (Appendix G). However, no significant differences were seen between groups when women were asked whether their treatment experiences for osteoporosis were good (Table 55). In the other trial where significant differences were seen in the intervention group, when examining the proportion of patients with more than 80 percent adherence, patient satisfaction with knowledge transfer was measured by self-report. The trial found no significant differences, suggesting insufficient strength of evidence (Table 55).[144]

Table 55. Decision aid interventions for musculoskeletal diseases: strength of evidence

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Decision aid vs. usual care	1; 100 (100)	Medication adherence	RCT Low	Unknown	Indirect	Imprecise	Various outcomes with varied measures Insufficient
	1; 100 (100)	Persistence	RCT Low	Unknown	Indirect	Imprecise	No statistically significant difference Insufficient
	1; 100 (100)	Initiation of therapy	RCT Low	Unknown	Indirect	NR	Insufficient
	1; 100 (NR)	Patient satisfaction	RCT Low	Unknown	Indirect	Imprecise	No statistically significant difference Insufficient

Abbreviations: NR = not reported; RCT = randomized controlled trial; vs. = versus.

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

Description of Included Studies

Overview

Four trials examined interventions designed to improve medication adherence in populations that had unspecified or multiple chronic conditions.[145-148] We rated one trial as having a low risk of bias[146] and the other three as having medium risk of bias.[145,147,148]

This section includes trials that are not featured in other sections of this KQ. Specifically, this section includes trials with populations that had unspecified chronic conditions or multiple chronic conditions. Multiple chronic conditions does not refer to coexisting conditions, unless the conditions are unspecified, in which case multiple unspecified conditions may be present simultaneously. Explicitly mentioned coexisting conditions (such as, for example, studies of patients with diabetes and hypertension as comorbidities) are included in KQ 4, which deals with vulnerable populations.

Population

We included here trials that populations with various multiple or unspecified chronic conditions. In trials that specified multiple conditions, the disorders included diabetes, hypertension, hyperlipidemia, and depression.

Intervention

In three of these four trials, the interventions included interaction with a pharmacist, a pharmacy outreach program, medication-related education (conducted by a pharmacist via telephone conversations with the patient), and a problem-solving intervention.[145-147] In the fourth, an interdisciplinary case management intervention formed the basis for what the authors termed as a "primary intensive care" intervention.[148]

Comparator

The comparator in each case was a usual-care control group (essentially a care environment that followed a typical standard of care for that group of patients). The specific components of usual care varied considerably because each trial had a different combination of chronic diseases and different intervention components. In the trial involving an interdisciplinary care environment, usual care was care directed by the primary care provider and 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.[148] Usual care in one trial was described as regular filling of prescriptions as requested by patients, without the pharmacist contact that the intervention included.[145] In another trial with pharmacist contact, usual care included routine review of medication and counseling by a nurse before discharge.[146] In the fourth trial, usual care included pharmacist evaluation of prescribed medications and clinical outcomes, but the pharmacist did not provide any form of counseling or advice to the patient.[147]

Outcome and Timing

None of the four trials reported on the initiation of therapy. All trials examined and reported adherence-related outcomes,[145-148] measured in different ways. Three trials relied on self-report.[146-148] A fourth assessed medication adherence using pharmacy refill data.[145] In one trial, exactly when outcomes were measured was unclear, although the references to "during the intervention year" indicated that various measurements were taken during the intervention or immediately after it.[148] In another, outcomes were measured at the completion of intervention (which was at the 12-month mark).[147] In one, medication adherence outcomes focused on whether the patient had taken each medication as prescribed on the previous day.[146] Finally, one trial measured outcomes during the interventions, when pharmacists contacted the patients, but the exact timing was unclear.[145]

Setting

One trial was done in nine pharmacies where pharmacists either called patients or faxed physicians.[145] One trial was conducted among patients who were discharged from one of four teams on the general medicine service of a hospital and were under the care by a hospital physician or resident.[146] A third trial was conducted within the primary care center of a hospital[148] The fourth trial was conducted in community-based physician offices.[147]

Applicability

Applicability of interventions examined is limited in several ways. First, the level of involvement of pharmacists in the intervention arm was appreciably greater than the currently accepted level of pharmacist involvement.[145] Second, the intensity (duration and frequency of contact) of the multidisciplinary intervention may be high for routine or common use.[148]

Key Points

Overview

- Of the four trials, none significantly improved medication adherence (low strength of evidence of no benefit) (Table 56). The evidence suggests that pharmacy outreach, education, and problem-solving interventions (all pharmacist-led) have no benefit (low

strength of evidence of no benefit). The case management intervention, called the "primary intensive care" intervention, did not improve adherence (insufficient evidence).

Table 56. Unspecified or multiple chronic conditions: summary of findings

Type of Intervention	Study	Adherence: Measure, Followup Period Overall Result (+/=/-) and Timing	Additional Outcomes: Outcome Overall Result (+/=/-) and Timing
Pharmacy outreach	Nietert et al., 2009[145] N=3048	= Time-to-refill (days) = Filled prescription for any qualified medication in the same chronic disease classification as the index medication, within 30 days of index date = Filled prescription for any qualified medication in the same chronic disease classification as the index medication, within 60 days of index date = Filled prescription for any medication, within 30 days of index date	NA
Education	Schnipper et al., 2006[146] N=178	= Medication adherence score on previous day = Number of patients nonadherent with at least one medication	NA
Problem-solving intervention	Taylor et al., 2003[147] N=81	= Medication adherence	NA
Case management intervention	Sledge et al., 2006[148] N=96	= Medication adherence score	NA

Abbreviations: (+) = statistically significant difference favoring intervention arm(s); (=) = no statistically significant difference; (-) = statistically significant difference favoring comparison arm; N = number; NA = not applicable.

Pharmacist-Led Outreach, Education, and Problem-Solving Interventions

- Medication adherence: Three trials (dominated by one with a large sample size [more than 3,000 patients analyzed] did not significantly improve medication adherence (low strength of evidence for no benefit). The large trial, in a post hoc analysis, reported that its physician-directed intervention arm may be inferior to usual care in improving time to refill for medications (insufficient evidence).

Case Management Intervention

- Medication adherence: The "primary intensive care" trial did not improve medication adherence (insufficient strength of evidence).

Detailed Synthesis of Interventions for Unspecified or Multiple Chronic Conditions

Four trials, each dealing with populations with unspecified or multiple chronic conditions, met the inclusion criteria for our review (Table 57).[145-148] One trial was directed at patients,[147] one at patients and providers,[145] one at patients and systems, [146] and one (with a multidisciplinary approach), was directed at systems-level change.[148] No trial found statistically significant differences in adherence between the intervention and control groups (Table 58 and Table 59).[145-148]

Table 57. Unspecified or multiple chronic conditions: detailed medication outcomes

Type of Intervention	Study N per Group	Sample and Setting	Intervention Groups	Intervention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Pharmacy outreach	Nietert et al., 2009[145] G1: 1,018 G2: 1,016 G3: 1,014	Patients with prescription for one of multiple chronic conditions, with least two refills remaining Nine pharmacies within a medium-sized grocery store chain	G1: Phone patient intervention G2: Fax physician intervention G3: Usual care		Time-to-refill (days from index date[a] to date of refill or end of study)	Pharmacy refill data	NA	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	NR
					Filled prescription for any qualified medication in the same chronic disease classification as the index disease,[b] within 30 days of index date[a]	Pharmacy refill data	NA	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	NA
					Filled prescription for any qualified medication in the same chronic disease classification as the index disease,[b] within 60 days of index date[a]	Pharmacy refill data	NA	Adjusted G1: Hazard ratio (HR, 97.5% CI), 0.86 (0.68 to 1.08) G2: HR, 97.5% 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	NA
					Filled prescription for any medication, within 30 days of index date[a]	Pharmacy refill data	NA	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	NA

Table 57. Unspecified or multiple chronic conditions: detailed medication outcomes (continued)

Type of Inter-vention	Study N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Education (pharma-cist-led)	Schnipper et al., 2006[146] Medication adherence score on previous day: G1: 92 G2: 84 Number of patients nonadherent: G1: 67 G2: 62	Discharged patients from general medicine service of hospital Hospital setting	G1: Pharmacist intervention involved review of medication regimen and followup call with patient G2: Routine review of medication orders by a ward-based pharmacist and medication counseling by a nurse at the time of discharge	Pharmacist counseling at the time of discharge with followup call 3 to 5 days after discharge	Medication adherence score on previous day (0 to 100; 100 indicates complete adherence with all medications)	Self-report	NR	G1: 88.9 (0.71 to 1.00) G2: 87.5 (0.73 to 1.00) 95% CI, NR p= 0.91	NR
					Number of patients nonadherent	Self-report	NR	G1: 36 (54%) G2: 33 (53%) 95 % CI, NR p>0.99	NR
Problem-solving (pharma-cist-led)	Taylor et al., 2003[147] G1: 33 G2: 36	Adults at participating clinics at high risk for medication-related adverse events Community-based physician offices	G1: Usual medical care, and pharmaco-therapeutic interventions by a pharmacist during regularly scheduled office visits G2: Standard medical care without pharmaceutical care	Patient met with pharmacist for 20 minutes prior to seeing physician	Medication adherence: (Took ≥80% of all medications in past month)	Self-report	G1: 84.9 (6.7) G2: 88.9 (5.8)	12 months: Mean (SD) compliant patients G1: 100 G2: 88.9 (6.3) 95% CI, NR p= 0.115	

Table 57. Unspecified or multiple chronic conditions: detailed medication outcomes (continued)

Type of Inter-vention	Study N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Case Manage-ment	Sledge et al., 2006[148] G1: NR G2: NR	Adults with ≥two medical or surgical hospital admissions Primary care center of an urban, academically affiliated hospital	G1: Comprehensive interdisciplinary medical and psychosocial assessment (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	2- to 3-hour visit that include compre-hensive interdis-ciplinary assess-ment Case manage-ment for 1 year in addition to usual care	Medication adherence score	Self-report	G1: 1.4 G2: 1.3 p = nonsignfi-cant	G1: NR G2: NR p = nonsignificant	NR

[a]Index date: the first date during the study period when the patient was seven days overdue
[b] Index disease: the chronic disease associated with the prescription on the index date
Abbreviations: CI = confidence interval; G = group; N = number; NA = not applicable; NR = not reported; PCP = primary care physician.

Table 58. 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 interventions (pharmacy outreach, education and problem solving) vs. usual care	3; 3307 (3269)	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

Abbreviations: N = number; NR = not reported; RCT = randomized controlled trial.

Table 59. Case management 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
Case management vs. usual care	1; 96(75)	Medication Adherence	RCT Medium	Unknown	Indirect	Imprecise	No significant difference in medication adherence score across arms Insufficient

Abbreviations: N = number; NR = not reported; RCT = randomized controlled trial.

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

This KQ evaluates the effect of policy-level interventions on medication adherence. We describe included studies, present key points for the body of evidence, and give a detailed synthesis of included studies. Appendix G presents information concerning clinical and economic outcomes, respectively.

Description of Included Studies

Overview

Five studies evaluated the effects of policy interventions on medication adherence.[149-153] Four of these studies were nonexperimental studies that used cohort designs and had a medium risk of bias. One study used an RCT design with low risk of bias.[153]

Population, Intervention, and Comparator

Four studies examined the effect of reduced medication copays on medication adherence. The remaining policy study investigated the impact of Medicare Part D on medication adherence among adults ages 65 or older with hyperlipidemia, hypertension, and/or diabetes.

Of the four copay studies, one RCT tested the effect of eliminating copays for brand-name and generic medications in four classes—angiotensin-converting-enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, and 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins) for patients after their discharge from a hospital for a myocardial infarction.[153] The study excluded individuals if they were enrolled in a health savings account or were 65 years of age or older. All participants received medical and prescription drug coverage through Aetna, and randomization was performed at the plan level. In addition to assessing the impact of reduced medication copays on adherence, this trial examined the effect of the policy change on clinical outcomes, including major vascular events and revascularization, and on patient and insurer prescription drug and nondrug spending.

Three other cohort studies examined the effect of reduced medication copays. One study evaluated the effects of reduced copays for medications in five classes—ACE inhibitors, ARBs, beta-blockers, diabetes medications, statins, and inhaled corticosteroids—for employees and covered dependents of a large company that used a specific disease management program.[149] This study was limited to adults ages 18 to 64 years. It compared the outcomes of 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.

Another study examined the effects of reduced copays for statins and clopidogrel (an antiplatelet medication) for beneficiaries of Pitney Bowes, a large company located in New Jersey.[150] Although this study did not impose age restrictions, the mean age ranged from 53.8 to 67.5 years across groups. This study compared outcomes of 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

The third study examined the effect of a value-based insurance design program implemented by Blue Cross Blue Shield of North Carolina.[152] This program reduced copays for brand-name medications used to treat diabetes, hypertension, hyperlipidemia, and heart failure for all of the insurer's enrollees; it eliminated copays for generic medications for enrollees whose employer opted into the program. The study compared outcomes of individuals whose employer opted into the program with those of individuals whose employer did not join the program. Because copays in the two groups differed only for generic medications, the investigators hypothesized that changes in adherence to brand-name drugs would be similar across the two groups but that individuals who participated in the program would exhibit greater changes in adherence to generic medications.

The remaining study investigating a policy-level intervention examined the impact of Medicare Part D on medication adherence among adults ages 65 or older with hyperlipidemia, hypertension, and/or diabetes.[151] The study restricted participants to those who were continuously enrolled in a large Pennsylvania insurer's Medicare Advantage products between 2003 and 2007.[151] 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 insurer. Thus, individuals in these three groups experienced an improvement in coverage when Medicare Part D was introduced. The study had a comparison group of individuals with retiree health insurance that almost always provided more generous coverage for prescription medications than that 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.

Outcome and Timing

In three of the cohort studies, the investigators tracked medication adherence for 1 year before and 1 year after the change in copay using 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.[149,150,152] The other cohort study tracked the MPR for 4 years, 2 years before and 2 years after the introduction of Medicare Part D.[151] The trial tracked participants for up to 3 years following randomization; the median duration of followup was 394 days.[153]

Applicability

We regarded all five studies as broadly applicable to these types of policy changes and outcomes. We assessed four of the studies as broadly applicable to the remaining criteria considered (i.e., population, comparator). However, we considered the remaining (nonexperimental) study as potentially less applicable to population and comparator because it was limited to individuals who had been continuously enrolled in a Medicare Advantage plan from 2004 through 2007.[151] In 2004, only 13 percent of Medicare beneficiaries were enrolled in such plans.[154]

Key Points

- All five studies found statistically significant differences in adherence between the intervention and comparison groups following implementation of policies decreasing copays or improving prescription drug coverage for all medications except inhaled corticosteroids (moderate strength of evidence for benefit).
- In two studies,[149,150] 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. In another study, medication adherence decreased over time in the comparison group and remained stable in the intervention group, accounting for the between-group difference observed.[152]
- Among patients with cardiovascular disease, consistent results from four observational studies and one RCT suggest that policy interventions can improve medication adherence (moderate strength of evidence of benefit).
- Among patients with diabetes, consistent results from three observational studies suggest that policy interventions can improve medication adherence (moderate strength of evidence for benefit).
- Among patients taking inhaled corticosteroids, results from one study did not show a benefit of reduced copays (insufficient evidence).
- Results from one RCT (low risk of bias) suggest that eliminating copays for preventive medications following a myocardial infarction can decrease the risk of fatal and nonfatal vascular events (insufficient strength of evidence for benefit).

Detailed Synthesis

Four policy-level studies examined effects of reduced medication copays on adherence to medications used to treat cardiovascular diseases (Table 60).[149,150,152,153] All four studies (three cohort; one RCT) performed analyses using MPR or PDC as a continuous measure and found

statistically significant between-group differences, favoring the intervention group, that ranged from 1.31 to 6.2 percentage points.

In two of these studies, medication adherence decreased over time in both intervention and comparison groups.[149,150] One study reported MPR scores for statins and clopidrogel ranging across study groups from about 80 percent to 87 percent at baseline and from about 63 percent to 67 percent at followup.[150] In another study, adherence decreased among individuals in the comparison group and remained stable among those in the intervention group.[152] Finally, the RCT gave no information about baseline adherence.[153] Thus, we cannot determine whether the between-group differences observed were caused by improvements in adherence in the intervention group or declines in adherence in the control group.

Two studies dichotomized the medication adherence measure at (a) below 0.8 or (b) at or above 0.8.[150,153] In the cohort study, individuals in the intervention group had 17 percent to 20 percent greater odds of high adherence than individuals in the comparison group immediately following the copay reduction.[150] Thereafter, the magnitude of the between-group difference remained stable over time. In the RCT, the odds of high adherence were between 31 percent and 41 percent higher in the intervention group relative to the control group across the medication classes examined.[153] This RCT found a 14 percent reduction in the risk of first fatal or nonfatal vascular events among individuals in the reduced copay group (Appendix G). In addition, patients in the reduced copay group spent less than those in the control group for prescription drugs and nondrug medical services. However, overall spending by the insurance provider was similar for the two groups (Appendix G).

Two cohort studies examined effects of reduced medication copays on adherence to medications for diabetes and reported findings similar to those for cardiovascular diseases (Table 60).[149,152] For example, in one of these studies, adherence to diabetes medications decreased from approximately 67 percent at baseline to 60 percent at final followup among individuals in the reduced copay group; by contrast, among individuals in the comparison group, medication adherence decreased from approximately 79 percent at baseline to 68 percent at final followup. Thus, the between-group difference observed at followup could be attributed to the slower rate of decline in MPR in the intervention group relative to the comparison group. In addition, at the last assessment the comparison group had a higher mean MPR than the intervention group. In the other study, individuals in the comparison group had a decline in adherence of about 4 percentage points, whereas individuals in the intervention group had stable adherence over time.[152]

One study examined the effect of reduced copays on adherence to inhaled corticosteroids.[149] Lower copays had no effect on adherence to medications in this class (Table 60).

In three of the observational studies, comparison groups differed on numerous characteristics from the intervention group.[149,150,152] In addition, one of the studies lacked sufficient detail to permit us to evaluate fully the analytic methods used.[149] In another study, medication copays increased for clopidogrel in the comparison group.[150] 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. However, the RCT evaluating the effect of reduced medication copays on adherence reported findings very consistent with those reported in the observational studies.[153] Therefore, we rated the strength of evidence supporting a beneficial effect of reduced medication copays on medication adherence as moderate (Table 61).

Table 60. Policy interventions: medication adherence

Author, Year	N per Group	Sample; Setting	Intervention Groups	Intervention Dose	Measure (Range, Direction)	Source	Baseline	Followup
Chernew et al., 2008[149]	For diabetes drugs: 2004 (pre) G1: range 919 to 1,245 G2: range 3,596 to 4,185 2005 (post) G1: range 1,056 to 1,306 G2: range 3,535 to 4,072 For all other drugs: N: NR	Adults, ages 18 to 64 years; employee health plan	G1: Employer-based health insurance plan implemented policy to reduce copays for five chronic medication classes as part of a disease management program. G2: No reduction in copays	Copays for generics were reduced to zero, copays for brand-name medications were reduced by half of previous value	Change in MPR (0 to 100%)	Prescription claims data	69.5 68.4 68.3 53.0 31.6	Diabetes drugs: 4.02, p<0.001 ACE inhibitors or ARBs: 2.59, p<0.001 Beta blockers: 3.02, p<0.001 Statins: 3.39, p<0.001 Inhaled corticosteroids: 1.86, p<0.134
Choudhry et al., 2010[150]	G1: 2,051 G2: 779 G3: 38,174 G4: 11,627	Patients with prescription claims for a statin or clopidogrel; pharmacy benefits management organization	G1: Pitney Bowes employees and beneficiaries with diabetes or vascular disease G2: Pitney Bowes employees and beneficiaries prescribed clopidogrel G3: Beneficiaries of BCBS of NJ G4: Beneficiaries of BCBS of NJ	G1: Elimination of copayments for statins G2: Lowered copayments for clopidogrel G3: No change in copayments for statins G4: No change in copayments for clopidogrel	Change in PDC (0 to 100%)	Prescription claims data	NR NR	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

Table 60. Policy interventions: medication adherence (continued)

Author, Year	N per Group	Sample; Setting	Intervention Groups	Intervention Dose	Measure (Range, Direction)	Source	Baseline	Followup
					Odds of PDC ≥ 0.80	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

Table 60. Policy interventions: medication adherence (continued)

Author, Year	N per Group	Sample; Setting	Intervention Groups	Intervention Dose	Measure (Range, Direction)	Source	Baseline	Followup
Zhang et al., 2010[151]	Diabetes G1: 247 G2: 304 G3: 2,214 G4: 1,253 Hyperlipidemia G1: 418 G2: 647 G3: 5,093 G4: 3,027 Hypertension: G1: 980 G2: 1,234 G3: 8,380 G4: 4141	Older adults enrolled in Medicare Part D Advantage products; Medicare enrollees	G1: No drug coverage prior to Medicare Part D G2: Some drug coverage before Medicare Part D with a $150 quarterly cap on plan payment G3: Some drug coverage before 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 to $20 per monthly prescription. No change in benefits during study	Implementation of Medicare Part D	Change in MPR (0 to 100%):	Prescription claims data	 57.0 77.3 75.4 81.8 47.3 57.6 62.3 74.4 62.4 81.6 82.7 85.1	Estimate (95% CI) Diabetes drugs 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) Hyperlipidemia drugs 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 drugs 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)
					Odds of MPR ≥ 0.80	Prescription claims data	 39.7 68.0 62.0 70.6 27.5 39.2 42.1 57.4	**Adjusted odds ratio (95% CI)** Diabetes drugs 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) Hyperlipidemia drugs 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)

Table 60. Policy interventions: medication adherence (continued)

Author, Year	N per Group	Sample; Setting	Intervention Groups	Intervention Dose	Measure (Range, Direction)	Source	Baseline	Followup
Zhang et al., 2010[151] (continued)							47.0 73.3 74.9 78.4	Hypertension drugs 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)
					Change in average number of pills for condition taken per day	Prescription claims data		Estimate (95% CI)
							0.98 1.12 1.11 1.29	Diabetes drugs 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)
							1.26 1.48 1.52 1.65	Hypertension drugs 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)

Table 60. Policy interventions: medication adherence (continued)

Author, Year	N per Group	Sample; Setting	Intervention Groups	Intervention Dose	Measure (Range, Direction)	Source	Baseline	Followup
Maciejewski et al., 2010[152]	**Metformin** G1: 5,077 G2: 2,826 Diuretics G1: 15,605 G2: 9,137 ACE inhibitors G1: 14,250 G2: 7,668 Beta blockers G1: 11,137 G2: 6,343 Statins G1: 18,346 G2: 10,162 Calcium channel blockers G1: 7,191 G2: 4,099 ARBs G1: 7,445 G2: 4,514 Cholesterol absorption inhibitors G1: 4,019 G2: 2,291	Individuals continuously enrolled in a BCBS of North Carolina health insurance plan between January 2007 and December 2008	G1: Eliminated copays for generic medications used to treat diabetes, hypertension, hyperlipidemia, and congestive heart and reduced copays for brand-name medications used to treat these conditions G2: Reduced copays for brand-name medications used to treat the conditions listed above. No change in copays for generics	Elimination of copays for generic medications used to treat the conditions specified	**Adjusted change in MPR** (0 to 100%)	Prescription claims records	NR	**Estimate, p-value** Metformin: 3.80, p < 0.001 Diuretics: 3.26, p < 0.001 ACE inhibitors: 2.87, p < 0.001 Beta blockers: 2.48, p < 0.001 Statins: 1.81, p < 0.001 Calcium channel blockers: 1.46, p < 0.01 Angiotensin-receptor blockers: -0.10, NS Cholesterol absorption inhibitors: -1.04, NS

Table 60. Policy interventions: medication adherence (continued)

Author, Year	N per Group	Sample; Setting	Intervention Groups	Intervention Dose	Measure (Range, Direction)	Source	Baseline	Followup
Choudhry et al., 2011[153]	**G1: 2,845** G2: 3,010	Individuals with recent myocardial infarction who had health insurance through Aetna	G1: Eliminated copays for brand-name and generic statins, beta blockers, ACE inhibitors, and ARBs G2: No change in copays	Elimination of copays for generic and brand-name medications in classes specified	**MPR** (0 to 100%)	Prescription claims records	NR	**Mean (SD)** ACE inhibitor or ARB: G1:41.1 (39.8) G2:35.9 (38.1) Absolute Difference as reported in article (95% CI): 5.6 (3.4 to 7.7) Mean (SD) Beta-blocker: G1: 49.3 (37.5) G2: 45.0 (36.6) Absolute Difference as reported in article (95% CI): 4.4 (2.3 to 6.5) Mean (SD) Statin: G1: 55.1 (37.7) G2: 49.0 (37.3) Absolute Difference (95% CI): 6.2 (3.9 to 8.5) Mean (SD) All classes combined: G1: 43.9 (33.7) G2: 38.9 (32.7) Absolute Difference (95% CI): 5.4 (3.6 to 7.2)

Table 60. Policy interventions: medication adherence (continued)

Author, Year	N per Group	Sample; Setting	Intervention Groups	Intervention Dose	Measure (Range, Direction)	Source	Baseline	Followup
					Odds of MPR ≥ 0.80	Prescription claims records	NR	**ACE inhibitor or ARB:** G1: 27.7 G2: 22.9 OR (95% CI): 1.31 (1.14 to 1.49) Beta blockers: G1: 30.7 G2: 25.2 OR (95% CI): 1.32 (1.16 to 1.49) Statins: G1: 38.6 G2: 31.6 OR (95% CI): 1.37 (1.20 to 1.56) All classes combined: G1: 12.1 G2: 8.9 OR (95% CI): 1.41 (1.18 to 1.67)

Abbreviations: ACE = angiotensin-converting-enzyme; ARBs = angiotensin-receptor blockers; BCBS = Blue Cross/Blue Shield; CI = confidence interval; G = group; MPR = medication possession ratio; N = number; NJ = New Jersey; NR = not reported; NS = not significant; OR = odds ratio; PDC = proportion of days covered; Ref = reference; SD = standard deviation.

Table 61. Policy interventions: strength of evidence by condition

Condition and Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Direct-ness	Precision	Magnitude of Effect/Strength of Evidence
Diabetes							
Improved prescription drug coverage vs. Unchanged prescription drug coverage	3; ~20,000 (~20,000)	Medication adherence	Medium	Consistent	Direct	Precise	Gaining coverage for diabetes medications 17.9 MPR points Reduced copay or improvement of previous coverage About 4 MPR points Moderate
Cardiovascular Disease							
Improved prescription drug coverage vs. unchanged prescription drug coverage	5; >70,000 (>70,000)	Medication adherence	Medium	Consistent	Direct	Precise	Magnitude of effect varies depending on the degree to which coverage is improved Moderate
	1 5,855 (5,855)	Death from cardiovascular causes	Low	Unknown	Direct	Precise	Nonstatistically significant reduction in risk Insufficient
	1 5,855 (5,855)	Rate of first vascular event or revascularization	Low	Unknown	Direct	Precise	Nonstatistically significant decrease in rate Insufficient
	1 5,855 (5,855)	Rate of first vascular event	Low	Unknown	Direct	Precise	14% decrease in rate Insufficient
	1 5,855 (5,855)	Patient total spending	Low	Unknown	Direct	Precise	26% decrease in relative spending Low
	1 5,855 (5,855)	Insurer total spending	Low	Unknown	Direct	Precise	Nonstatistically significant decrease in relative spending Low
Inhaled corticosteroids reduced medication copay vs. unchanged medication copay	1; NR (NR)	Medication adherence	High	Unknown	Direct	Imprecise	Insufficient

Abbreviations: MPR = Medication possession ratio; NR = not reported.

The final policy-level study examined the impact of Medicare Part D on adherence to medications used to treat patients with diabetes, hyperlipidemia, and hypertension (Table 60).[151] In contrast to the findings from the 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. However, among patients with some coverage for prescription medications before implementation of Medicare Part D, the estimated differences in MPR scores ranged from 2.5 to 7.3. The study found similar differences for medications used to treat hypertension and diabetes. 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 (moderate strength of evidence of benefit) (Table 61).

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

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 62 studies (68 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 raised clients' self-awareness more than did physician or pharmacist-delivered interventions.

Detailed Synthesis of Intervention Characteristics

Overview of Characterization of Interventions

In these sections we characterize 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 62 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. In the following sections 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 one another, 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.[74]

Intervention Target

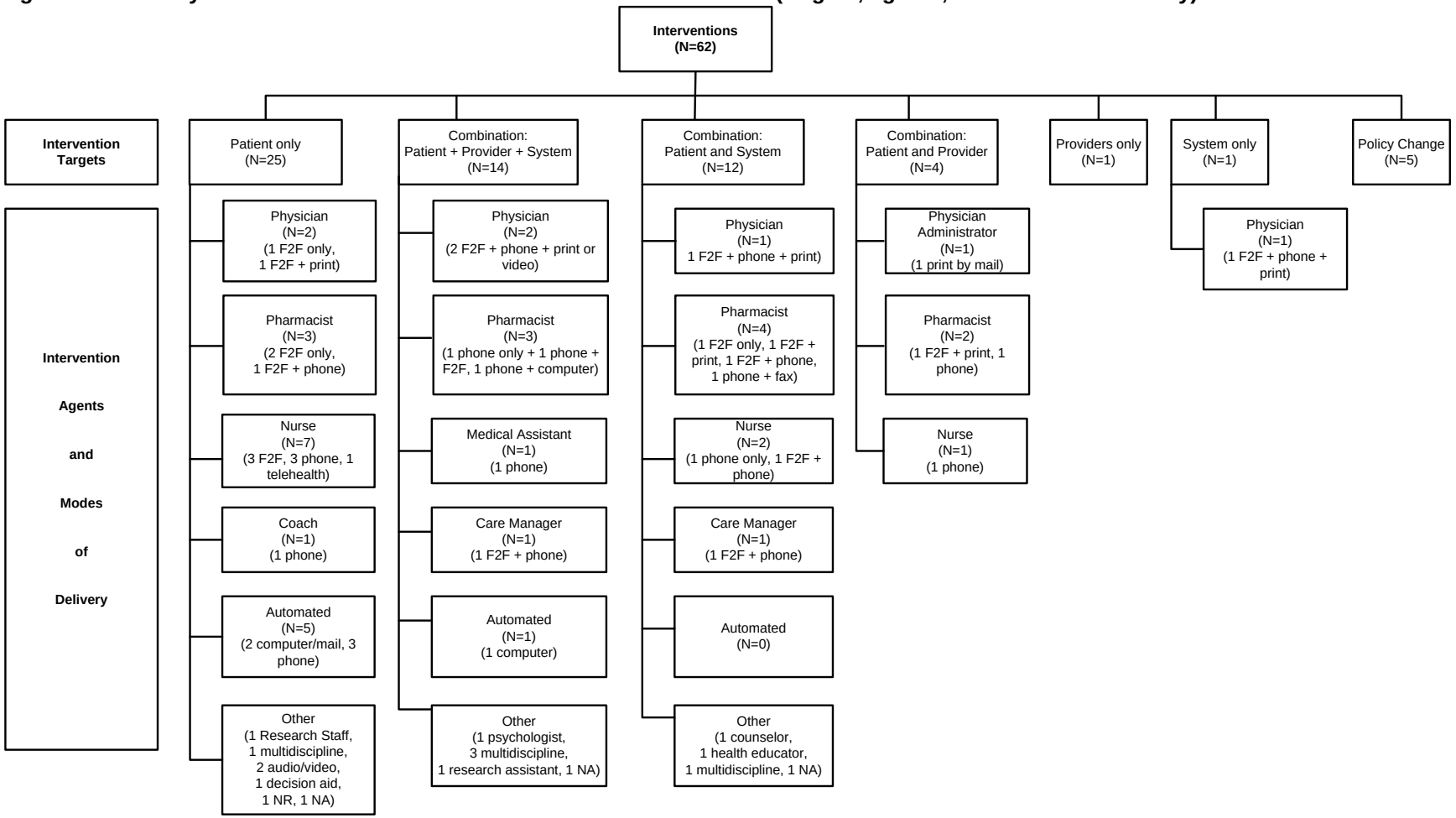
Intervention target refers to the person, people, health system, or policy to which intervention activities are directed. Although the ultimate goal of adherence interventions is to improve patient behavior (i.e., taking medications), the interventions may do this by directly targeting providers, patients, health systems, health policies, or some combination of these four. In the 62 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 (40.3 percent of interventions); (2) combination of patients, providers, and systems (22.5 percent); (3) combination of patients and systems (19 percent); (4) combination of patients and providers (6 percent); (5) providers only (1.6 percent); (6) systems only (1.6 percent); and (7) health policy changes (8 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 include provider, system and policy 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 62 interventions reviewed (in order of frequency), 12 (19 percent) were delivered by pharmacists, 10 (16 percent) were delivered by nurses, 7 (11 percent) were delivered by physicians (including one physician administrator), 6 (10 percent) by an automated system, 5 (8 percent) by a multidisciplinary team, 2 (3 percent) by care managers, 1 (1.6 percent) by a medical assistant, and 1 (1.6 percent) by a health coach. Other agents included a health educator, a psychologist, a counselor, research staff members, and some audio-video materials, including decision aids. For 9 interventions (15 percent), including 4 of the 5 directed at policy changes, a specific agent of delivery was not applicable or identifiable. For one policy change intervention, the health insurer was the agent of delivery.

Interventions that targeted "patients only" tended to use automated (21 percent) and nurse (29 percent) agents more than did interventions that targeted combinations of factors. In contrast,

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



Abbreviation: F2F = face-to-face; assist = assistant; NA = not applicable; NR = not reported

few interventions with a combination of targets used automated systems (4 percent) or nurses (8 percent) as agents. Physicians or pharmacists delivered interventions that targeted "patients only" (22 percent) less often than did 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 62 interventions, 26 (42 percent) of the interventions involved only 1 delivery mode and 22 (35 percent) utilized 2. Five (8 percent) used 3 delivery modes and four (6 percent) used 4 modes to deliver the intervention.

Twenty-nine of the interventions (47 percent) involved at least some face-to-face contact although, of these 29, 21 (72 percent) combined face-to-face with additional modes of delivery, such as phone contact, print materials, computer, video, or other materials. Similarly, 30 interventions (48 percent) delivered at least some of the intervention by phone; however, only 13 (43 percent) of these involved "phone-only" delivery modes. Twenty or about one third (32 percent) of the interventions used print material, although only 6 (30 percent) of these 20 utilized print materials alone, all of which were mailed to their targets. Six of the 62 interventions (10 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 (1.6 percent) used a medication dosing aid device to deliver part of the intervention and another used a telehealth delivery device. Another intervention that simply involved a novel blister packaging mechanism did not have clear agent or mode of delivery.

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 62, 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 62, in six studies, the intervention did not involve specific contact points (such as with a systems or policy change) and in four 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 five to six 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.

Table 62. 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[122]	Asthma	F2F	5	NS	150 minutes	7 weeks
Berg et al., 1997[121]	Asthma	F2F	6	NS	720 minutes	7 weeks
Janson et al., 2009[123]	Asthma	F2F	5	q 2 to 4 weeks	150 minutes	14 weeks
Wilson et al., 2010[127]	Asthma	F2F, phone	5	NS	210 minutes	9 months
Weinberger et al., 2002[125]	Asthma	F2F, print	.> 1 NS	q month	NS	NS
Weinberger et al., 2002[125]	Asthma	F2F, print	> 1 NS	q month	NS	NS
Bender et al., 2010[120]	Asthma	Phone	2-3	NS	~10 to 15 minutes	10 weeks
Bender et al., 2010[120]	Asthma	Phone	2-3	NS	~10 to 15 minutes	10 weeks
Schaffer & Tian, 2004[124]	Asthma	Audio or book	1	NA	30 to 60 minutes	NS
Williams et al., 2010[126]	Asthma	Computer	> 1 NS	q 2 weeks	NS	NS
Murray et al., 2007[116]	Heart failure	F2F, print	NS	NS	NS	9 months
Rich et al., 1996[117]	Heart failure	F2F, print	NS	NS	NS	NS
Fulmer et al., 1999[115]	Heart failure	Phone, videophone	30	q day	~120 minutes	6 weeks
Ross et al., 2004[118]	Heart failure	Computer	NS	NS	NS	12 months
Bogner & de Vries, 2010[87]	Depression, Diabetes	F2F, phone	5	NS	120 minutes	4 weeks
Bogner & de Vries, 2008[101]	Depression	F2F, phone	5	NS	120 minutes	4 weeks
Katon et al., 2001[130] Ludman et al., 2003[131] Von Korff et al., 2003[132]	Depression	F2F, phone, print, DVD	9	NS	150+ minutes	12 months
Katon et al., 1999[136] Katon et al., 2002[137]	Depression	F2F, phone, print, DVD	2+	NS	75 minutes	NS
Katon et al., 1996[135]	Depression	F2F, phone, print, videos	8	q 2 to 12 weeks	360+ minutes	24 weeks
Katon et al., 1995[134]	Depression	F2F,print, video	4	q 8 to 10 days	105 minutes	6 weeks
Simon et al., 2006[129]	Depression	Phone	3	q 1 to 2 months	60 minutes	3 months
Capoccia et al., 2004[133]	Depression	Phone	18	q 1 to 2 weeks	270 minutes	12 months
Pyne et al., 2011[138]	Depression	Phone [for Pat] EMR [for Prov]	> 1 NS	q 2 to 4 weeks	NS	NS
Rickles et al., 2005[128]	Depression	Phone	3	NS	45 minutes	3 months
Hoffman et al., 2003[139]	Depression	Print, mail	6	q month	NS	6 months
Weymiller et al., 2007[93] Jones et al., 2009[94]	Diabetes	F2F	1	NA	NS	NA
Pearce et al., 2008[91]	Diabetes	F2F	1	NA	30 minutes	NA

Table 62. 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[89]	Diabetes	F2F, phone	16	NS	240+minutes	12 months
Mann et al., 2010[92] Choice	Diabetes	F2F, print	1	NA	6 minutes	NA
Mann et al., 2010[92] Choice	Diabetes	F2F, print	1	NA	6 minutes	NA
Grant et al., 2003[88]	Diabetes	Phone, computer	6	Q 2 weeks	111 minutes	3 months
Okeke et al., 2009[140]	Glaucoma	F2F, phone, video, dosing aid device	10	NS	NS	3 months
Schectman et al., 1994[98]	Hypercholesterolemia	Phone	5	NS	NS	28 days
Stacy et al., 2009[99]	Hypercholesterolemia	Phone, mail, print	3	NS	NS	6 months
Guthrie, 2001[95]	Hypercholesterolemia	Phone, mail	5	Per schedule	NS	6 months
Johnson et al., 2006[96]	Hypercholesterolemia	Computer; mail	3	NS	NS	6 months
Hunt et al., 2008[105]	Hypertension	F2F	1-4	NS	NS	NS
Lee et al., 2006[78]	Hypertension, Hyperlipidemia	F2F	7	q 2 months	240 minutes	12 months
Vivian, 2002[113]	Hypertension	F2F	6	NS	NS	6 months
Carter et al., 2009[104]	Hypertension	F2F, phone	1.6	q 3 months	NS	6 months
Solomon et al., 1998[111] Gourley et al., 1998[112]	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[106] Bosworth et al., 2007[107]	Hypertension	Phone	12	Q 2 months	NS	24 months
Bosworth et al., 2005[108]	Hypertension	Phone	12	Q 2 month	NS	24 months
Friedman et al., 1996[109]	Hypertension	Phone	24	Weekly	96 minutes	6 months
Johnson et al., 2006[110]	Hypertension	Computer; mail	3	q 3 months	NA	6 months
Schneider et al., 2008[100]	Hypertension	Packaging	NA	NA	NA	NA
Rudd et al., 2009[142]	Inflammatory arthritis	F2F, phone, print	2	q months	40 minutes	NS
Powell et al., 1995[97]	Multiple chronic conditions	Mail	1	NA	30 minute	NA
Zhang et al., 2010[151]	Multiple chronic conditions	NA	NA	NA	NA	NA
Chernew et al., 2008[149]	Multiple chronic conditions	NA	NA	NA	NA	NA
Nietert et al., 2009[145]	Multiple chronic conditions	Telephone, fax	NS	NS	NS	NS

Table 62. 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
Wakefield, et al, 2011[103]	Multiple Unspecified Chronic Conditions	Telehealth	157	Daily	NS	6 months
Choudhry et al., 2010[150]	Multiple conditions	NA	NA	NS	NA	NA
Berger et al., 2005[141]	Multiple sclerosis	Phone	6 to 12	q 2 to 4 weeks	NS	3 months
Waalen et al., 2009[143]	Osteoporosis	F2F, phones, print	varied	q month	5-minute/call	NS
Taylor et al., 2003[147]	Other	F2F, print	>1 NS	NS	20-minute/visit	12 months
Sledge et al., 2006[148]	Other	F2F, phone, print	> 13	Monthly phone	180+ minutes	1 year
Schnipper et al., 2006[146]	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.

Total Amount of Contact Time

Thirty-three studies (53 percent) did not specify the total dose intensity of the interventions; another 7 (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 or the number of contacts but not the amount of time per contact (Table 62). Among the studies that provided this information, the amount of time varied widely among interventions, ranging from 6 minutes to 12 hours. Of 26 trials 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 38 interventions (61 percent) that did, the duration ranged widely from 4 weeks to 2 years, with 6 months' duration as the mode: 11 (29 percent) of the 38 studies lasted 6 months. Another 7 (18 percent) of programs with known duration lasted 12 months, 5 (about 13 percent) lasted 3 months, and only 2 (5 percent) lasted 2 years. Duration of the remaining 13 interventions (34 percent) fell between 4 weeks and 12 months. In general, asthma and heart failure medication adherence interventions appeared to be of slightly shorter duration compared with those for diabetes, depression, hypertension, and hypercholesterolemia.

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.[74] 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 to 9), few interventions involved only one component. Most interventions with only a single component were not delivered by a specified agent but 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: 16 interventions (27 percent) had 3 components, 21 (35 percent) had fewer than 3, and only 3 interventions (5 percent) had more than 6 components. Table 63 shows the reported number of interventions that had each number of components (1 through 9) 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 63. Reported number of interventions with each number of components (1–9) by delivery agent

Number of Components	Auto	Multidisciplinary	Nurse	Pharmacist	Physician	Other	Nonspecified Agent	Total
1	0	0	0	0	0	3	6	9
2	2	0	1	5	2	1	1	12
3	2	1	1	4	1	5	2	16
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 (77 percent). About 44 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 used facilitation techniques, including 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 (20 percent) of the interventions. Activities such as modeling, practicing task-specific skills, verbal persuasion, making plans for coping responses, setting graded tasks, and reattributing success and failure were coded as self-efficacy enhancements.

Other components that were present in some of the interventions reviewed included intention formation activities (18 percent), action control (17 percent), addressing attitudes (12 percent), motivational interviewing (10 percent), stress management (3 percent), and social influence (3 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 64, 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 two of nine delivered by nurses and four of nine 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.

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 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.

Table 64. Number of interventions with each of nine key components most commonly observed in adherence interventions reviewed by agent of delivery

	Nine Key Intervention Components											
	Knowledge, Without Awareness	**Knowledge, With Awareness**	**No Knowledge**	**Self-Efficacy**	**Facilitation**	**Maintenance**	**Intentions, Action Control**	**Intentions, Action Control**	**No Intentions, Action Control**	**No Intentions, No Action Control**	**Motivational Interviewing**	**Attitude Changes**
Agent of Delivery												
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=10)	1 (10%)	7 (70%)	2 (20%)	5 (50%)	6 (60%)	4 (40%)	2 (20%)	2 (20%)	1 (10%)	4 (40%)	2 (20%)	1 (10%)
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%)

Abbreviation: N = number.

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 65. Shared decisionmaking 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 decisionmaking, 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 65. 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

Abbreviation: NA = not applicable.

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

Description of Studies

Overview

We found five articles comprising only four 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, one involved patients with diabetes mellitus, and one involved patients with hypertension.[93,94,103,115,127] 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.[93,103,115,127]

Population

All four 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.[93,94] One study was restricted to poorly controlled asthma.[127] 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.[115] The study of hypertension included adult Veterans Administration (VA) patients with hypertension and type 2 diabetes.[103]

Interventions

Interventions varied widely in their approaches to improving adherence; all were directed at patients.

The asthma studies focused on providers and systems in addition to patients.[127] They evaluated shared decisionmaking between patients and clinicians.[127]

The diabetes, heart failure, and hypertension studies were directed solely at patients.[93,94,103,115] The heart failure study included two intervention arms and one control arm.[115] 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).[93,94] 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.[115] The hypertension study tested a nurse case manager home telehealth intervention [103] at two different doses of the same intervention (high and low intensity levels of monitoring and education).

Comparator

For KQ 3b, the relevant comparator was a modification of the intervention. In the asthma study[127] for example, shared decisionmaking (in which the patients' preferences and values were assessed and taken into account in selecting recommended treatment) was compared with traditional physician-driven 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.[93,94] 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.[115] The hypertension study compared the two intensity levels of the nurse-case management home telehealth intervention[103] and to each other (high and low intensity levels of monitoring and education) in addition to a usual-care control arm.

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 SABA using refill data.[127]

The study of diabetes patients used a single self-report item to ask about medication taking using a 7-day recall period[93] to count the number of people who missed no doses.[93] The heart failure studies measured adherence via MEMS caps.[115]

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 decisionmaking intervention effects on forced expiratory volume (FEV-1).[127] Other outcomes of interest included the Asthma Therapy Assessment Questionnaire (ATAQ) and health-related quality of life.[127]

The hypertension study[103] assessed adherence to antihypertensives using the 4-item Morisky scale.

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 decisionmaking study recorded 2-year adherence information for an intervention with an active component that lasted 9 months.[127] 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,[115] which lasted 6 weeks. The hypertension trial of telemonitoring case management assessed adherence at 6-month followup[103].

Setting

The asthma study worked within health systems.[127] The diabetes study recruited from a metabolic specialty clinic where the intervention was delivered.[93,94] The heart failure study focused on a population recruited from an urban home health agency and ambulatory care clinic[115] but delivered the intervention in patients' homes.[115] The hypertension study recruited patients from one large VAMC although the intervention itself was administered remotely. [103]

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.[115] The hypertension study applicability is limited because it was conducted in one unique health care system, the VA.[103]

Key Points

Overview

- All four 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 (Table 66).
- Only one of four studies demonstrated a statistically significantly effect for direct comparisons of specific intervention components on improving medication adherence.

Table 66. Medication adherence interventions with direct comparisons: summary of findings

Type of Intervention	Studies, N Randomized	Adherence: Measure, Followup Period Overall Result (+/=/-) and Timing	Additional Outcomes: Outcome Overall Result (+/=/-) and Timing
Case management	Wakefield et al., 2011[103] N=302	Morisky scale scores at 6 months	NA
Shared decision-making vs. usual care	Wilson et al., 2010[127] N=612	+ Medication acquisition ratio for all drugs, 1 and 2 years + Acquisition of inhaled corticosteroids, 1 year + Acquisition of beclomethasone, 1 year and 2 years Acquisition of long-acting beta-agonists, 1 and 2 years	+ Forced expiratory volume, 1 year + Symptom improved: acquisition of short acting beta-agonists, 1 and 2 years + Asthma control, 1 year + Quality of life, 1 year Health care utilization: asthma-related visits
Decision aids	Mann et al., 2010[92] N=150 Weymiller et al., 2007[93] Jones et al., 2009[94] N=98	= Percentage with high adherence on Morisky scale at 3 and 6 months + Number missing no medication doses in prior week at 3 months = Percentage using statins at 3-month followup	NA Patient satisfaction items + Amount of information = Clarity of information + Helpfulness of information = Would recommend to others deciding on statins = Would prefer similar approach for other treatment choices + Overall acceptability
Reminder calls	Fulmer et al., 1999[115] N=60	+ Adherence rate, 8 weeks	= Quality of life at 10 weeks

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

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 no evidence of difference exists between mode of delivery (insufficient).

High Versus Low Intensity Case Management by Telemonitoring With Education

- Medication adherence: Evidence from a single study suggests no evidence of difference exists between the high and low dose of a telemonitoring and educational intervention (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 (Table 67); 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 68).[127] 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 (Appendix G).[127] 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. 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. No differences between clinical- and shared decision-making arms were found for quality of life or asthma-related visits.

Table 67. Medication adherence interventions with direct comparisons: medication adherence

Study	N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Shared decision-making	Wilson et al., 2010[127] G1: 204 G2: 204 G3: 204	Adults ages 18 to 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	Five face-to-face, phone, 9 months	Medication acquisition ratio for all asthma medications (total days supply acquired in a year/365 days)	Pharmacy refill data	NR	Means at 1 year: G1: 0.67 G2: 0.59 G3: 0.46 (95% CIs): G1 to G3: (0.13 to 0.280), p=0.0001 G1 to G2: (0.01 to 0.15), p=0.0029 G2 to G3: (0.05 to 0.20), p=0.0008	Mean differences at 2 years: G1 to G3: 0.03 G1 to G2: 0.04 G2 to G3: -0.01 (95% CIs): G1 to G3: (-0.05 to 0.11) G1 to G2: (-0.04 to 0.12) G2 to G3: (-0.09 to 0.07)
					Medication acquisition ratio for inhaled corticosteroids (total days' supply acquired in a year/365 days)	Pharmacy refill data	NR	Means at 1 year G1: 0.59 G2: 0.52 G3: 0.37 (95% CIs):NR p: G1 to G3: 0.0001 G1 to G2: 0.017 G2 to G3: 0.0001	NR
					Acquisition of beclo-methasone canister equivalents	Pharmacy refill data	NR	Means at year 1: G1: 10.9 G2: 9.1 G3: 5.2; (95% CIs): G1 to G3: (4.5 to 7.0), p=0.0001 G1 to G2: (0.57 to 0.31), p=0.005 G2 to 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 to G3: (1.2 to 3.8), p=0.0002 G1 to G2: (0.04 to 2.7), p=0.04 G2 to G3 (-0.18 to 2.4), p>0.05

Table 67. Medication adherence interventions with direct comparisons: medication adherence (continued)

Study	N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Shared decision-making (continued)					Medication acquisition for long-acting beta-agonists	Pharmacy refill data	NR	Mean difference at 1 year: G1 to G3: 0.11 G1 to G2: 0.09 G2 to G3: 0.01 (95% CIs): G1 to 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 to G3: 0.11 G1:G2: 0.09 G2 to G3: 0.01 (95% CIs): G1 to G3: (0.01 to 0.20) G1 to G2: (0.01 to 0.18) G2 to G3: (-0.08 to 0.11)
Decision aids									
Mann et al., 2010[92]	G1: NR G2: NR	Adult patients with diabetes mellitus Urban primary care clinic	G1: Statin choice decision aid G2: ADA print material	One face-to-face session + printed material	Percentage with "good adherence" on 8-item Morisky Adherence Scale **(0 to 100%)**	Self-report	Baseline NR	3 months: Overall: 70% G1: NR G2: NR 95% CI, NR p: No significant difference between groups	6 months: Overall: 80% G1: NR G2: NR 95% CI, NR p: No significant difference between groups
	G1: NR G2: NR				Percentage prescribed statin during baseline visit (0 to 100%)	Self-report	Baseline G1: 9% G2: 0% 95% CI, NR p=0.01		

Table 67. Medication adherence interventions with direct comparisons: medication adherence (continued)

Study	N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Weymiller et al., 2007[93] Jones et al., 2009[94]	G1: 33 G2: 29	Adults with Type 2 diabetes mellitus Metabolic specialty clinic	G1: Statin choice decision aid G1a: Research staff before visit G1b: Clinician during visit G2: Standard of care educational pamphlet control	One face-to-face session + printed material	Number missing no medication doses in the last week	Self-report	NR	3 months: G1: 31 G2: 23 Odds ratio (OR): 3.4 95% CI: 1.5, 7.5 p: NR	
	G1a: NR G1b: NR G2a: NR G2b: NR		G2a: Research staff before visit G2b: Delivered by clinician during visit		Number missing no medication doses in the last week, by mode of delivery	Self-report	NR	3 months: G1a: NR G1b: NR G2a: NR G2b: NR OR for delivery mode: 0.8 95% CI: 0.3, 2.6 p: NS	
	G1: 52 G2: 46				Percentage using statins at followup	Self-report	NR	3 months: N (%) G1: 33 (63%) G2: 29 (63%) 95% CI, NR p: NR OR: 1.4 95% CI: 0.8 to 2.4 p: NR	
Fulmer et al., 1999[115]	G1: 17 G2: 15 G3: 18	Adults >65 years with HF Urban Ambulatory	G1: Daily video reminder G2: Daily phone reminder G3: No reminder calls	Daily calls (Mon through Fri), 6-week duration	Compliance rates (0 to 100%, % of total pills taken)	MEMS	G1: 82% G2: 76% G3: 81%	8 weeks: G1: 84% G2: 74% G3: 57% (p<0.04) 95% CI: NR G1 + G2 vs. G3: F=4.08, p <0.05 G1 vs. G2:p>0.05	

Table 67. Medication adherence interventions with direct comparisons: medication adherence (continued)

Study	N per Group	Sample and Setting	Intervention Groups	Inter-vention Dose	Measure (Range, Direction)	Source	Baseline	First Followup	Additional Followups
Case manage-ment	Wakefield et al., 2011[103] G1: NR G2: NR G3: NR	Adults with diabetes mellitus and HTN	G1: High-intensity: use of home telehealth device for blood pressure and glucose as well as education with nurse case management G2: Low–intensity: Similar to G1 intervention with lower intensity of educational content G3: Usual care	6 months, daily entries for BP and glucose	Morisky scale	Self-report	NR	6 months: G1: NR G2: NR G3: NR p: Per text no significant difference between groups; all groups improved from baseline; NR if statistically significant	NR

Abbreviations: aOR = adjusted odds ratio; BP = blood pressure; CI = confidence interval; G = group; HF = heart failure; HTN = hypertension; NS = not specified; NR = not reported; OR = odds ratio; SD = standard deviation; SE = standard error.

Table 68. 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. clinical decision making	1; 612 (612)	Medication adherence	RCT Medium	Unknown	Direct	Precise	Difference in medication acquisition ratio for all asthma medications: 0.13 to 0.21 (range) Low for benefit
	1; 612 (551)	Pulmonary function	RCT Medium	Unknown	Direct	Precise	Difference in FEV1 percentage points: 2.7 to 3.4 Low for benefit
	1; 612 (612)	Symptom improvement	RCT Medium	Unknown	Direct	Precise	Difference in mean equivalents of SABA canister equivalents acquired at 2 years between shared decision-making and usual care: 1.6 Low for 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 to 0.4 Low for benefit
	1; 612 (612)	Health care utilization	NA	Unknown	Direct	Precise	Difference of 0.3 to 0.4 fewer asthma-related visits per year Low for benefit

Abbreviations: FEV1 = forced expiratory volume at 1 minute; NA = not applicable; RCT = randomized controlled trial; SABA = short-acting beta agonists.

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 67), suggesting insufficient strength of evidence (Table 69). This same study assessed medication persistence (the proportion of patients still on treatment at followup) but found no difference between the groups.[93]

Table 69. Decision aids for hypertension: 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.

Detailed Synthesis for Video and Telephone Reminders

Medication Adherence

Although the heart failure study showed statistically significant improvement in at least one measure of medication adherence in the intervention group compared to the control group,[115] the difference between the two intervention groups, which differed by mode of delivery, was not statistically significant (Table 67), resulting in insufficient strength of evidence (Table 70).

Table 70. 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.

Detailed Synthesis of High and Low Intensity Telemonitoring and Education

Medication Adherence

All three arms had improved adherence at 6-month followup but the difference between the groups was not statistically significantly different from each other (Table 67).[103] The difference between the two intervention groups, which varied by dose, was not statistically significant, resulting in insufficient strength of evidence (Table 71).

Table 71. Hyperlipidemia: strength of evidence for education and behavioral support interventions

Intervention	Number of Studies; Subjects (Analyzed)	Outcome	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Hyperlipidemia: Education + behavioral support	5; 18,492 (9,411 + NR in 1 study)	Medication adherence, persistence	RCT Medium	Consistent	Direct	Imprecise	Variable measures (self-report, pharmacy refill) with variable outcomes Low

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

Key Question 4. Vulnerable Populations

Description of Included Studies

Overview

Fifteen studies tested interventions intended to improve medication adherence in vulnerable populations.[78,87,89,100,101,103,115,117,121,134,135,137,138,147,151] We present PICOTS 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 various complex situations such as those with low health literacy, coexisting conditions or 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 12 of these 15 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.[78,87,89,100,101,103,115,117,121,138,147,151] In the remaining three studies, the vulnerable populations were subgroups within the overall study sample;[134,135,137] two studies conducted subgroup analyses based on major depression[134,135] and one study focused on moderate- to high-severity depression.[137]

Among the 12 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,[78,100,115,151] and one defined elderly as those who were more than 70 years of age.[117] In four studies, the vulnerable population involved patients with depression. Of these, two involved patients with depression and diabetes,[87,89] one included patients with depression and HIV,[138] and one focused on patients with depression and hypertension.[101] In another study, the vulnerable population included patients with diabetes and hypertension.[103] In two studies, the vulnerable population involved patients from rural communities.[121,147] One of the studies that examined coexisting conditions also included Black primary care patients.[87]

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.[89,117,134,135,137,138] One study examined a collaborative care model with HIV and mental health clinicians;[138] three others examined collaborative care provided by a primary care physician and a psychologist and psychiatrist;[134,135,137] 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;[117] and one described an individualized management of depression that involved psychiatric consultations and group services among other features.[89]

The same team conducted two integrated care interventions that dealt with patients with depression.[87,101] The studies were identical except for the coexisting condition on which the

study focused: diabetes[87] or hypertension.[101] In addition to telephone calls and care coordination, the care management interventions in these studies included multiple in-person visits.

Six other studies focused primarily on the patient.[78,100,115,121,147] 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.[100] 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.[78] After this initial phase was completed, meetings with pharmacists and use of medications aids both continued but the medication education continued only on an as-needed basis.[78] A third study used a video reminder call for one group of patients and a telephone reminder call (without video) for the other group.[115] One study examined the effectiveness of case management—specifically a nurse-administered self-management program on compliance.[121] Another study examined the use and effectiveness of a nurse-managed home telehealth intervention to improve outcomes.[103] The final study in this group examined the effect of a pharmaceutical intervention.[147]

Finally, a single study focused on policy change, specifically, the impact of Medicare Part D prescription drug coverage on medication adherence.[151]

Comparator

All studies compared the active intervention with usual-care or control-group populations.[78,87,89,100,101,103,115,117,121,134,135,137,138,147,151] In certain studies in which 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.[89,134-138] 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.[117] In the two integrated care studies, usual care was described generally as routine care appropriate to the setting.[87,101] In one study in which the intervention group received blister-packaged medication, the usual care group received traditional bottles of medication.[100] Similarly, in a study that combined medication education, pharmacist followup, and adherence aid use in the intervention, the usual care group did not receive education or blister-packaged medication.[78] In another study, the comparator group did not receive the reminder calls that the intervention groups received.[115] 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.[151] In one study, usual care was minimally described.[121]

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 members of a vulnerable population.[78,87,89,100,101,103,115,117,121,134,135,137,138,147,151] 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[78,87,101,138,147] and 95 percent or greater.[138] Other types of medication adherence outcomes included MPRs,[100,151] adherence to adequate dosage from pharmacy refill data,[137] self-reported medication adherence,[121,135] percentage of patients receiving adequate dosage of medication,[134] percentage of patients who had prescription filled on time,[100] percentage of

patients who were adherent in specified time frames,[78] monitoring devices (MDI Chronolog) used to assess compliance with inhaler use,[121] and percentage of prescribed doses taken using the MEMS.[115] In one study, adherence was measured by two scales, one of which was the Self-Reported Medication Taking scale[155] and the other was a validated regimen adherence scale.[103]

Most studies reported on medication adherence outcomes during the intervention period, immediately following it, or within a period after the conclusion of the intervention that ranged from a few weeks to 12 months.[87,89,100,101,103,117,121,134,135,138,147] In one study, adherence was monitored during a 2-week pre-intervention phase in addition to measurements at the end of the study and 2 weeks following the end of the study.[115] One study reported on long-term outcomes up to 28 months after initial randomization was complete.[137] 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 RCT.[78] In this particular study, outcomes obtained at 14 months were considered to be 6-month outcomes for the RCT portion.[78] 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.[151]

Setting

Two integrated care studies were set in community-based primary care clinics.[87,101] Several collaborative care studies took place within primary care clinics belonging to the Group Health Cooperative in Washington State.[89,134,135,137] One collaborative care study was conducted in a university teaching hospital[117] and another was set in a VA HIV clinic.[138] The blister-packaging study was conducted in ambulatory care clinics in Columbus, Ohio, and Tucson, Arizona.[100] Another study was set in a university-affiliated tertiary care U.S. military medical center.[78] 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.[115] In the self-management intervention, participants were recruited directly from the community.[121] The case management intervention study focused on a primary care population.[103] In another study, the setting was community-based physician offices in rural Alabama.[147] The policy change study was conducted by examining administrative data of patients enrolled in a large insurer's Medicare Advantage products.[151]

Key Points

- Interventions to improve medication adherence among vulnerable populations had varying strength of evidence. 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 four populations considered. The interventions, the diseases being treated, and the methods for measuring medication adherence outcomes differed considerably between studies.
  - Medication adherence improved for the following: patients with major depression, severe depression, multiple chronic conditions, or with depression and hypertension as coexisting conditions; Black patients with depression and diabetes as coexisting conditions; and elderly patients with diabetes, hyperlipidemia, heart failure, or hypertension (all low strength of evidence).
  - Medication adherence did not improve for patients with depression and HIV as coexisting conditions (insufficient evidence).

- Medication adherence did not improve for patients with coexisting diabetes and depression, except for one study of Black patients with coexisting diabetes and depression (insufficient evidence).
- Medication adherence did not improve for patients with coexisting hypertension and diabetes (insufficient evidence).
- Medication adherence for patients from rural communities improved for patients in one study but did not improve for patients in another study (insufficient evidence).
- No evidence was available for the following: (a) racial and ethnic minorities with the exception of those who identified as Black race; (b) populations of low literacy, low incomes, and no or poor health insurance (insufficient evidence).

Detailed Synthesis

The following synthesis presents results for each vulnerable populations considered. Table 72 presents strength-of-evidence grades.

Table 72. Vulnerable populations: strength of evidence

Intervention Vulnerable Population, Condition Details	Number of Studies; Subjects (Analyzed)	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Medicare Part D Elderly patients with diabetes, hypertension or hyperlipidemia	1; 20,889 (20,889)[151]	Before-after study Medium	Unknown	Direct	Precise	Varied measures and magnitude Low
Collaborative intervention Diabetes patients with depression	1; 329(329)[89]	RCT Medium	Unknown	Direct	Imprecise	Insufficient
Blister packaging Elderly patients with hypertension	1; 93(85)[100]	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 heart failure	1; 60(50)[115]	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

Table 72. Vulnerable populations: strength of evidence (continued)

Intervention Vulnerable Population	Number of Studies; Subjects (Analyzed)	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Multidisciplinary intervention: collaborative care Elderly patients with heart failure	1; 156(156)[117]	RCT Medium	Unknown	Direct	Precise	Varied measures and magnitude Low
Multidisciplinary intervention: collaborative care Patients with major depression	2: 370 (177+NR for one study):[134,135]	RCT Medium	Consistent	Direct	Precise	Varied measures and magnitude Low
Multidisciplinary intervention: collaborative care Patients with severe depression	1228 (at 6 months: 229; at 28 months: 187)[137]	RCT Medium	Unknown	Direct	Precise	Varied measures and magnitude Low
Integrated care Patients with depression with hypertension	1;64 (64)[101]	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 Black patients with depression and diabetes	1; 58 (58)[87]	RCT Medium	Unknown	Direct	Precise	Difference in percentage points of patients with ≥80% adherence to an antidepressant: 13.8 Difference in percentage points of patients with ≥80% adherence to hypoglycemic agent: 13.8 Low
Collaborative care Patients with depression and HIV	1; 276 (249)[138]	RCT Medium	Unknown	Direct	Imprecise	Insufficient

Table 72. Vulnerable populations: strength of evidence (continued)

Intervention Vulnerable Population	Number of Studies; Subjects (Analyzed)	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect and Strength of Evidence
Pharmacy care program Elderly patients with multiple conditions	1; 159 (159)[78]	RCT Medium	Unknown	Direct	Precise	Difference in percentage points in medication adherence: 26.4 Difference in percentage points of patients with ≥80% adherence to all medications: 75.7 Low
Asthma self-management Patients from a rural community	1; 55 (55)[121]	RCT Medium	Unknown	Direct	Precise	Difference in percentage points in medication adherence: 17 Low
Case management nurse-managed home telehealth Patients with diabetes and hypertension	1; 394 (NR)[103]	RCT	Unknown	Direct	Imprecise	NR Insufficient
Pharmaceutical care Patients from a rural community	1; 81 (69)[147]	RCT	Unknown	Direct	Imprecise	Difference in percentage points in medication adherence: 11.1 Insufficient

Abbreviations: G = group; NR = not reported; RCT = randomized controlled trial.

Racial and Ethnic Minorities

Among Black patients with depression and diabetes, an integrated care intervention improved adherence to medications for both diabetes and depression.[87] This study also dealt with coexisting conditions.

Populations With Persistent Disease, Severe Disease, or Coexisting Conditions

One study demonstrated statistically significant improvement in medication adherence compared with usual care for populations with either major or minor depression at 7 months after randomization.[134] 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.[135]

In another study, adherence outcomes were recorded during 6-month intervals through a 28-month period; overall differences by intervention arms were recorded at 3 and 6 months after randomization.[137] Among patients who were severely depressed at baseline, the intervention arm continued to show benefits of the intervention on medication adherence at 12 months; among those with moderately severe depression, improvement in adherence in the intervention arm was seen for the 6 months after randomization.[137]

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.[138] Among patients with diabetes who suffered from depression, a collaborative intervention did not improve medication adherence to ACE-inhibitors, oral hypoglycemic agents, and lipid-lowering agents.[89] Among patients ages 50 years or older with depression and hypertension, an integrated care intervention improved adherence to medications for both hypertension and depression.[101] Among Black patients with coexisting conditions of depression and diabetes, an integrated care intervention improved adherence to medications for both diabetes and depression.[87] This study falls under the minority population category. In a case management intervention for patients with comorbid diabetes and hypertension, the intervention improved medication adherence, although improvement was seen across all groups, without significant differences between groups.[103]

Elderly Populations

Among elderly patients with diabetes, Medicare Part D improved adherence to medications for prevention of cardiovascular disease. This effect was much greater among those who had had no prior insurance coverage before Medicare Part D than for those who did have some prior coverage.[151] Among elderly patients with hyperlipidemia, Medicare Part D improved adherence to lipid-lowering medications; the pattern was the same as for cardiovascular disease greater impact among those without (rather than with) prior insurance coverage.[151]

Among elderly patients with hypertension, an intervention involving daily-dose blister packaging improved adherence.[100] A video- or telephone-based intervention improved medication adherence among elderly patients with heart failure when compared with a usual-care control group.[115] A multidisciplinary intervention improved medication adherence outcomes among elderly patients with heart failure.[101,117] In one study among elderly patients taking at least four medications for chronic diseases, a pharmacy care program significantly improved medication adherence.[78]

Rural Populations

A self-management intervention for asthma directed at patients in a rural population produced statistically significant improvement in adherence in the intervention arm compared with the control arm.[121] A pharmaceutical intervention directed at patients in rural Alabama, however, did not report any significant difference in adherence between the intervention and control arms.[147]

Key Question 5. Harms

Description of Included Studies

Three RCTs addressed unintended consequences, or harms, associated with interventions to improve medication adherence (Table 73).[98,104,116]

Table 73. Harms: trial characteristics

Author, Year N at Randomization	Population Setting	Intervention and Comparator
Carter et al., 2009[104] 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 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[116] 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[98] 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 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

Abbreviations: G = group; N = number.

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 values or diastolic blood pressure values within specific ranges (systolic blood pressure, 140 to 179 mm Hg; diastolic blood pressure, 90 to 109 mm Hg).[104] It included hypertensive patients who had diabetes if their systolic blood pressure was between 130 to 179 mm Hg or diastolic blood pressure between 90 to 109 mm Hg.[104] Another trial included patients ages 50 years or older who had a confirmed diagnosis of heart failure.[116] 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 at a VAMC, participants were patients with hyperlipidemia who required treatment with either niacin or BAS therapy but had not taken either before.[98]

Intervention

One trial evaluated a collaborative model including care from a physician and a pharmacist.[104] In another trial the intervention was pharmacist-led.[116] In the third trial, the intervention was based on telephone contact that trained health care professionals made to patients.[98]

Comparator

In the trial using the collaborative model, the comparison group received no clinical pharmacist intervention.[104] In the pharmacist-led trial, the control group comparison was the absence of clinical pharmacist intervention but the patients received usual care.[116] 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.[116] In the telephone-based trial, the comparison group received no telephone intervention.[98]

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; it centered on symptoms that were suggestive of adverse events.[104,156] 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 to 188): *not at all* (score: 0); a little bit (score: 1); *somewhat* (score: 2); *quite a bit* (score: 3) or *very much* (score: 4).[156] 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 patients who experienced an adverse events or medication error using a program that identified adverse events from the medical record system.[116] They did not indicate the exact timing of these measurements.[116] In the VAMC 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.[98]

Setting

The trials were conducted in various settings: community-based family medicine residency programs,[104] a university-affiliated ambulatory care practice,[116] and a VA lipid clinic.[98]

Key Points

- In the collaborative model trial, the questionnaire-based symptom score, which was indicative of adverse events, decreased for both the intervention and control groups.[104] In the other two trials, the number of adverse events in the intervention group did not differ significantly from the number in the control group. In the ambulatory practice trial, adverse events included frequently occurring events such as cough or allergy related to ACE inhibitors; they 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).[98]
- 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[98,104] (Table 74). 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 post-study period.[116] In two of the three studies, the intervention group did not have a significantly different number of adverse events from the control group.[98,116] 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.[104] Therefore, among the three trials included, the number of adverse events did not differ between the intervention arms and the control arms;[98,116] in one case, the difference in adverse events favored the intervention arm.[104]

Table 74. Harms: adverse events outcomes

Author, Year N Analyzed	Adverse Event Outcome	Timing of Adverse Event Measurement and Data Source	Results
Carter et al., 2009[104] 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[116] G1: 112 G2: 192	Number of patients who had an adverse drug events or medication error	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[98] 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; CI = confidence interval; G = group; NR = not reported; NS = not significant; SD = standard deviation.

Discussion

This chapter 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 57 trials in 63 articles included in this comparative effectiveness review suggests that numerous pathways provide opportunities to improve medication adherence across clinical conditions. These approaches 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; such interventions often require some, or even a good deal of restructuring of typical approaches to health care delivery in the United States.

Despite such evidence about promising approaches to improving medication adherence, only a subset of these effective interventions relate better adherence with better health outcomes or other important end results. We found relatively little evidence linking improved adherence to improvements in other outcomes, such as biomarkers, morbidity, mortality, quality of life, quality of care, patient satisfaction, health care utilization, and costs.

Findings Specific to Clinical Conditions

The volume of evidence regarding improving medication adherence differs sharply by clinical condition. We found the greatest amount of evidence, in terms of numbers of trials or studies or numbers of subjects (or both), for hypertension and depression, followed by hyperlipidemia, asthma, and diabetes (Table 75). We did not find a substantial body of evidence testing varied approaches to inform several other clinical conditions. For musculoskeletal diseases, we found three trials that used interventions with no common features. Myocardial infarction, glaucoma, and multiple sclerosis had just one trial each. We found no eligible studies for cancer; reasons likely include the restrictions specified for this comparative effectiveness review to patient-administered medications and to outpatient settings. We found no eligible studies that explicitly focused on patients with adherence problems relating to polypharmacy, although a few studies included patients with two or more conditions and assessed adherence to more than one medication.

Collectively, the most consistent evidence was that various types of interventions improved medication adherence outcomes for hypertension, heart failure, depression, and asthma. These improvements were accompanied by improvements in systolic and diastolic blood pressure for case management and face-to-face education with pharmacists for hypertension; reduced emergency department (ED) visits and improved patient satisfaction for pharmacist-led multicomponent interventions for heart failure; improved symptoms, pulmonary function, health care utilization, and quality of life for shared decisionmaking; improved symptoms for case management for depression; and improved symptoms and patient satisfaction with medications and quality of care for collaborative care for depression. We generally graded these interventions

Table 75. Summary of results for patient, provider, and systems interventions (KQ 1)

Clinical Condition	Type of Intervention	Strength of Evidence for Medication Adherence	Number of Studies; n of Individuals (n Analyzed) Results	Strength of Evidence for Other Outcomes	Number of Studies; n of Individuals (n Analyzed) Results
Diabetes	Case management/collaborative care[87-89]	Low SOE of benefit for medication adherence	3; 507 (507) Varied measures and magnitude	Low SOE of benefit for HbA1C	1; 58 (58) 1.2 percentage points difference
Diabetes	Education with social support[91]	Insufficient for medication adherence	1; 199 (189) No stat sig difference	NA	NA
Diabetes	Health coaching[90]	Insufficient for medication adherence	1; 56 (49) No stat sig difference	NA	NA
Hyperlipidemia	Collaborative care[89]	Insufficient for medication adherence	1; 329 (117 on lipid- lowering meds) No stat sig difference	NA	NA
Hyperlipidemia	Decision aids[92-94]	Insufficient for medication adherence	2; 248 (98 + NR in 1 trial) Variable self-report measures with variable outcomes	Low SOE of benefit for patient satisfaction:	1; 98 (98) Variable self-report measures, some improvements for intervention group in specific areas
Hyperlipidemia	Education and behavioral support (phone or mail)[95-99]	Low SOE of benefit for medication adherence	5; 18,492 (9,411 + NR in 1 trial) Variable measures (self-report, pharmacy refill) with variable outcomes	NA	NA
Hyperlipidemia	Multicomponent (education face-to-face with pharmacist + blister packaging)[78]	Insufficient for medication adherence	1; 159 (159) Improved in intervention group over 6 months, outcome at risk of bias due to differing measurement frequency: (1) Percentage adherence (95.5% vs. 69.1%) (2) Percentage with $\geq$80% adherence (97.4 vs. 21.7)	Insufficient for LDL-C	1; 159 (135) No stat sig difference between groups

Table 75. Summary of results for patient, provider, and systems interventions (KQ 1) (continued)

Clinical Condition	Type of Intervention	Strength of Evidence for Medication Adherence	Number of Studies; n of Individuals (n Analyzed) Results	Strength of Evidence for Other Outcomes	Number of Studies; n of Individuals (n Analyzed) Results
Hypertension	Blister Packaging[100]	Low SOE of benefit for medication adherence and persistence	1; 93 (85) MPR: 6 percentage points difference between groups Percentage of patients who had prescriptions refilled on time: 14.3 percentage points difference between groups,	Insufficient for SBP+DBP; angina, MI, or stroke	1; 93 (85) No stat sig difference in change in SBP or DBP or in percentage of patients with reduced SBP, angina, MI, or stroke 29.8 percentage points difference in patients with reduced DBP at 12 months in intervention group
				Insufficient for health care utilization: ED visits + hospitalizations	1; 93 (85) No stat sig difference between groups for either outcome
Hypertension	Case management[101-103]	Low SOE of benefit for medication adherence	3; 516 (64 + NR in 2 studies) Two of three RCTs with stat sig difference in adherence: (1) MEMS ≥80% adherence: 46.8 percentage points more in experimental group than control group (2) MEMS adherence, mean: 11.3 percentage points higher in experimental group	Low SOE of benefit for SBP + DBP:	2; 214 (64 + NR in 1 study) Difference in SBP : - 8.5 to -14 mm Hg (range across studies) Difference in DBP: -3.1 to -9.2 mm Hg (range across studies)
Hypertension	Collaborative care[89,104,105]	Low SOE of no benefit for medication adherence	3; 1194 (785) No stat sig differences between groups	NA	NA
Hypertension	Education (face-to-face with pharmacist)[78,111-113]	Low SOE of benefit for medication adherence; insufficient for persistence	3; 348 (344) for adherence Variable outcomes for adherence, some stat sig differences favoring intervention 1; 56 (53) for refilling meds on time No stat sig difference between groups refilling meds on time	Moderate SOE of benefit for SBP	2; 292 (268) -6.4 or -8.9 mm Hg mean SBP difference
				Insufficient	2; 292 (268) 1.1 or -4.4 mm Hg mean DBP difference
				Insufficient for quality of life	1, 133 (NR) No stat sig differences for sexual dysfunction, dizziness, and headaches

Table 75. Summary of results for patient, provider, and systems interventions (KQ 1) (continued)

Clinical Condition	Type of Intervention	Strength of Evidence for Medication Adherence	Number of Studies; n of Individuals (n Analyzed) Results	Strength of Evidence for Other Outcomes	Number of Studies; n of Individuals (n Analyzed) Results
				Low SOE of benefit for patient satisfaction	1; 133 (130) Stat sig improvement in four of five questions
				Low SOE of benefit for hospital visits	1; 133 (124) 0.08 fewer hospital visits in intervention group
				Low SOE of benefit for contact with other health care providers	1; 133 (124) 0.41 fewer visits in intervention group
				Insufficient for ED visits	1; 133 (124) No stat sig difference
Hypertension	Education and behavioral support (telephone, mail, and/or video)[97,106-110]	Low SOE of benefit for medication adherence	5; 6,996 (5149 + NR in 2 studies) Multiple variable outcomes Two RCTs with stat sig difference in adherence showing 6 percentage points higher in intervention group from baseline to 6 months and greater adherence at 12 and 18 months, no numbers reported	Insufficient for SBP or DBP	1; 299 (267) No stat sig difference between groups in change from baseline to 6 months
Hypertension	Education with social support[91]	Insufficient for medication adherence	1; 199 (199) No stat sig differences between groups at 12 months	NA	NA
Hypertension	Risk communication[114]	Insufficient for medication adherence	1; 89 (89) No stat sig difference between groups at 3 months	NA	NA
Heart failure	Access to medical records[118]	Insufficient for medication adherence	1; 107; (NR) No significant difference at 6 or 12 months	NA	NA

Table 75. Summary of results for patient, provider, and systems interventions (KQ 1) (continued)

Clinical Condition	Type of Intervention	Strength of Evidence for Medication Adherence	Number of Studies; n of Individuals (n Analyzed) Results	Strength of Evidence for Other Outcomes	Number of Studies; n of Individuals (n Analyzed) Results
Heart failure	Case management[117]	Low SOE of benefit for medication adherence	1; 156 (156) Difference in percentage points for med adherence: 6.6 to 6.8 (range) Difference in percentage points for proportion with >80% adherence between groups: 15.7 to 16.3	Insufficient for all-cause hospital admission	1; 156 (156) No significant difference in multiple measures of all-cause readmission
Heart failure	Multicomponent pharmacist-led[116]	Low SOE of benefit for medication adherence	1; 314 (314 for MEMS caps, NR for MPR or self-report) 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 for MPR over 12 months: 4.2 No stat sig difference for self-report	Insufficient for quality of life	1; 314 (NR) No stat sig difference
				Low SOE of benefit for patient satisfaction	1; 314 (NR) Difference of 0.3 on 12-point validated questionnaire
				Low SOE of benefit for all-cause ED visits and all-cause ED+hosp	1; 314 (314) Difference of 0.52 mean all-cause ED visits and 0.69 mean all-cause ED+hosp between groups
				Insufficient for healthcare utilization for all-cause hospitalization, CV-related and HF-related events, costs	1; 314 (314) No stat sig difference
Heart failure	Reminder video and telephone calls[115]	Low SOE of benefit for medication adherence	1; 60 (50) Difference of 17 to 27 percent comparing video and phone to control in MEMS adherence over 8 weeks	Insufficient for quality of life	1; 60 (42) No stat sig difference

Table 75. Summary of results for patient, provider, and systems interventions (KQ 1) (continued)

Clinical Condition	Type of Intervention	Strength of Evidence for Medication Adherence	Number of Studies; n of Individuals (n Analyzed) Results	Strength of Evidence for Other Outcomes	Number of Studies; n of Individuals (n Analyzed) Results
Myocardial infarction	Education and behavioral support[119]	Low SOE of benefit for medication adherence; insufficient for persistence	1; 907(836) Percentage points mean increase in adherence over 9 months: 4.3% Percentage points difference with ≥80% adherence: 6% No stat sig difference for persistence	NA	NA
Asthma	Self-management[120-124]	Moderate SOE of short-term benefit in medication adherence	Difference in percentage points for adherence: 14 to 31	Insufficient for pulmonary function and inflammation markers	2; 152 (149) No stat sig difference
				Insufficient for symptom improvement	5; 303 (300) Varied measures and magnitude (inconsistent)
				Low SOE of no benefit for quality of life	4; 248 (245) Varied measures and magnitude (consistent)
Asthma	Shared or clinical decision-making[127]	Low SOE of benefit for medication adherence	1; 612 (612) Difference in medication acquisition ratio for all asthma medications: 0.13 to 0.21	Low SOE of benefit for pulmonary function	1; 612 (612) Difference in FEV1 percentage points: 2.7 to 3.4
				Low SOE of benefit for symptom improvement	1; 612 (612) Difference in mean equivalents of SABA canister equivalents acquired at 2 years between shared decisionmaking and usual care: 1.6
				Low SOE of benefit for quality of life	1; 612 (612) Difference in subscale scores on 5-item Mini Asthma Quality of Life Questionnaire: 0.3-0.4
				Low SOE of benefit for health care utilization	1; 612 (612) Difference of 0.3 to 0.4 fewer asthma-related visits per year

Table 75. Summary of results for patient, provider, and systems interventions (KQ 1) (continued)

Clinical Condition	Type of Intervention	Strength of Evidence for Medication Adherence	Number of Studies; n of Individuals (n Analyzed) Results	Strength of Evidence for Other Outcomes	Number of Studies; n of Individuals (n Analyzed) Results
Asthma or COPD	Pharmacist or physician access to patient adherence information[125,126]	Low SOE of no benefit for medication adherence	2; 3,811 (3,596) No stat sig difference	NA	NA
Depression	Case management[87,101,130-132]	Moderate SOE of benefit for medication adherence	3; 508 (437) Difference in percentage points for adherence or filling prescriptions over time: 9 to 15 (range across studies)	Moderate SOE of benefit for symptom improvement	3; 508 (437) Difference in CES-D scale: 7.0 to 9.4 (range across studies) Mean difference in SCL-20 (0 to 4 range) scores between groups across 12 months: 0.08
				Insufficient for self-reported disability	1; 386 (315) Varied measures, outcomes, time periods
Depression	Collaborative care[133-138]	Moderate SOE of benefit for medication adherence for telephone+in-person; insufficient for telephone only; insufficient for depression+HIV patients	3 (telephone and in-person); 598 (598) Difference in percentage points for adherence: 16.5 to 40.3 (range across studies) No stat sig difference for depression+HIV patients or telephone collaborative care only	Low SOE of benefit for symptom improvement for major depression of moderate depression; insufficient for severe or minor depression	Severe depression: 2; 214 (214) Minor depression: 1; 149 (149) Moderate depression: 2; 156 (156) Major depression: 1; 79 (79) Varied measures, outcomes, time periods
				Low SOE of benefit for patient satisfaction with antidepressants	2; 370 (370) Difference in percentage points in those rating antidepressants as helping somewhat to a great deal: 6.0 to 24.8 (range across studies)
				Insufficient for health care utilization	3; 598 (598) Varied outcomes, time periods, and consistency
				Insufficient for costs	1; 228 (228) No stat sig difference

Table 75. Summary of results for patient, provider, and systems interventions (KQ 1) (continued)

Clinical Condition	Type of Intervention	Strength of Evidence for Medication Adherence	Number of Studies; n of Individuals (n Analyzed) Results	Strength of Evidence for Other Outcomes	Number of Studies; n of Individuals (n Analyzed) Results
				Moderate SOE of benefit for patient satisfaction with quality of care	3; 598 (598) Difference in percentage points in those rating quality of care as good to excellent: 5.1 to 32.5 (range across studies) at 3 to 4 months; 16 at 6 months
Depression	Medication telemonitoring or telephone care[128,129]	Insufficient for medication adherence	2; 270 (255) No stat sig difference	NA	NA
Depression	Reminders to nonadherent patients and lists of nonadherent patients to providers[139]	Low SOE of benefit for medication adherence	1; 9,564 (9,564) Difference in percentage points for adherence; 1 to 3 (range across study)	NA	NA
Glaucoma	Multicomponent intervention[140]	Low SOE of benefit for medication adherence	1; 66 (66) Difference in adherence rate: 0.22	Insufficient for intraocular pressure	1; 66 (66) No stat sig difference
Multiple sclerosis	Counseling (software-based telephone)[141]	Low SOE of benefit for medication adherence	1; 435 (367) Difference in percentage points of patients who discontinued use of MS therapy:7.5	NA	NA
Musculoskeletal diseases	Decision aid[144]	Insufficient for medication adherence, persistence, initiation of therapy	1; 100 (100) Varied outcomes and measures	Insufficient for patient satisfaction	1; 100 (NR) No stat sig difference
Musculoskeletal diseases	Case management[142]	Insufficient for medication adherence	1; 127 (127) No stat sig difference	NA	NA
Musculoskeletal diseases	Virtual osteoporosis clinic[143]	Low SOE of benefit for medication adherence	1; 235 (211) Difference in percentage points of women using osteoporosis medication at 13 months: 23.7	Insufficient for patient satisfaction	1; 235 (211) No stat sig difference

Table 75. Summary of results for patient, provider, and systems interventions (KQ 1) (continued)

Clinical Condition	Type of Intervention	Strength of Evidence for Medication Adherence	Number of Studies; n of Individuals (n Analyzed) Results	Strength of Evidence for Other Outcomes	Number of Studies; n of Individuals (n Analyzed) Results
Multiple or unspecified chronic conditions	Case management intervention[145-147]	Low SOE of no benefit for persistence	3; 3307 (3269) No stat sig difference	NA	NA
Multiple or unspecified chronic conditions	Outreach, education, and problem-solving (pharmacist-led)[148]	Insufficient for medication adherence	1; 96 (75) No stat sig difference	NA	NA

Abbreviations: CES-D scale = Center for Epidemiologic Studies-Depression scale; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; DBP = diastolic blood pressure; ED = emergency department; FEV1 = forced expiratory volume at 1 minute; G = group; HF = heart failure; HbA1c = hemoglobin A1c;hosp = hospitalization; KQ = Key Question; LDL-C = low-density lipoprotein cholesterol; MEMS = medication event monitoring system; MI = myocardial infarction; MPR = medication possession ratio; NA = not applicable; NR = not reported; RCT = randomized controlled trial; SABA = short-acting beta agonists. SBP = systolic blood pressure; SCL-20 = Hopkins Symptom Checklist-20; SOE = strength of evidence; stat sig = statistically significant.

as beneficial with low-to-moderate strength of evidence, depending on the specific type of intervention. Of note, three clinical conditions (hypertension, heart failure, and depression) included some interventions for which evidence was insufficient due to lack of consistency or precision in the evidence (Table 76).

For asthma and hypertension, because of several studies of low or moderate risk of bias that failed to find an effect, we judged that two interventions provided evidence of no benefit: these two interventions included collaborative care for hypertension and patient or provider access to patient adherence data for asthma.

Trials in diabetes, hyperlipidemia, and musculoskeletal diseases found a single intervention indicating benefit for medication adherence. These trials focused on care coordination and collaborative care approaches for diabetes, education and behavioral support for hyperlipidemia, and a virtual clinic for osteoporosis; all other approaches did not produce improvements and were judged to be insufficient for lack of consistency or lack of precision in the results.

The least consistent evidence of improvement in medication adherence pertained to patients with multiple chronic conditions: three trials, using pharmacist-based outreach, education, and problem-solving approaches, provided evidence of no benefit for medication adherence, and findings from another trial, using case management, were insufficient.

We found the least evidence for myocardial infarction, glaucoma, and multiple sclerosis. Single trials in each of these clinical areas suggested low strength of evidence of benefit for medication adherence.

Findings Specific to Interventions

We identified 20 intervention approaches (Table 76) across the clinical conditions included in this comparative effectiveness review. Intervention approaches tested in patient populations with different clinical conditions (either single diagnoses of chronic illnesses or, in some cases, two or more such ailments) included case management, collaborative care, decision aids, education, reminders, and pharmacist-led multicomponent approaches. Our findings suggest that educational interventions and case management approaches offer the most consistent and voluminous evidence of improvements in medication adherence across varied clinical conditions. We found moderate strength of evidence for self-management interventions for asthma, which generally include strong educational components. Trials showing improvement with case management and educational interventions provided some evidence of improvement for other health outcomes. We found low strength of evidence of benefit from educational interventions for medication adherence for hypertension, hyperlipidemia, and myocardial infarction, and insufficient evidence for diabetes. We found low or moderate strength of evidence of benefit from case management for diabetes, hypertension, heart failure, and depression, insufficient evidence for musculoskeletal diseases, and low strength of evidence of no benefit for persistence for multiple chronic conditions.

Other promising approaches tested and found to be effective in more than one clinical area include reminders and pharmacist-led multicomponent approaches. Interventions such as shared decisionmaking and blister packaging were tested in a single clinical area with a single trial; without additional evidence, their widespread applicability is difficult to judge but may well hold promise.

Table 76. Summary of strength-of-evidence grades for medication adherence by type of intervention

Type of intervention	Diabetes	Hyper-lipidemia	Hyper-tension	Heart Failure	Myocardial infarction	Asthma	Depression	Glau-coma	MS	Musculo skeletal diseases	Multiple or unspeci-fied conditions
Blister packaging			MA: L(+) Pers: L(+)								
Case management	MA: L(+)		MA: L(+)	MA: L(+)			MA: M(+)			MA: INS	Pers: L(-)
Collaborative care (phone+ in person)	MA: L(+)	MA: INS	MA: L(-)				MA: M(+)				
Collaborative care (telephone only)							MA: INS				
Counseling (software-based telephone)									MA: L(+)		
Decision aids		MA: INS								MA, pers, Init: INS	
Education (face-to-face with pharmacist)			MA: L(+) Pers: INS								
Education+ behavioral support (phone, mail, and/or video)		MA: L(+)	MA: L(+)		MA: L(+) Pers: INS						
Education+ social support	MA: INS		MA: INS								
Health coaching	MA: INS										
Multicomponent interventions		MA: INS		MA: L(+)				MA: L(+)			
Outreach, education, and problem-solving											MA: INS
Pharmacist or physician access to patient adherence data						MA: L(-)					
Patient access to medical records				MA: INS							
Reminders				MA: L(+)			MA: L(+)				
Risk communication			MA: INS								
Self-management						MA: M(+)					
Shared or clinical decisionmaking						MA: L(+)					
Telemonitoring							MA: INS				
Virtual clinic										MA: L(+)	

Abbreviations: init= initiation of therapy; INS = insufficient; L(-) = low strength of evidence of no benefit; L(+) = low strength of evidence of benefit; M(+) = moderate strength of evidence of benefit; MA = medication adherence; MI = myocardial infarction; MS = multiple sclerosis; pers = persistence.

Some interventions may be most effective for a particular clinical condition. Collaborative care appeared to be effective primarily for patients with depression or with depression and diabetes; for other clinical conditions (hyperlipidemia and hypertension), the evidence was insufficient.

The categories noted above are shorthand for one or more key elements of very diverse interventions. As explained in earlier chapters, we opted not to try to impose any external taxonomy on these markedly different programs; none seemed suitable for capturing the underlying constructs or specific activities we encountered in this literature. 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, whereas the other did not. Thus, the inductive approach we used to identify types of interventions allowed us to group them in ways that seemed to reflect key similarities, but doing so limited our ability to draw firm conclusions about the effectiveness of *specific* intervention features. In addition, the trials that tested multicomponent efforts did not have multiple intervention arms that would have provided information about particular (individual) elements of the intervention effort. Nevertheless, we attempted to address this limitation through analyses for KQ 3, and those findings offer further insights on some common elements across these interventions.

Key Question 2. Effect of Policy Interventions on Medication Adherence and Other Outcomes

Five studies evaluated the effects of policy-level interventions on medication adherence, specifically for cardiovascular disease, diabetes, and respiratory conditions. One study was a randomized controlled trial (RCT). The other four studies used cohort designs. All of the studies 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 comparison of results.

All five 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.[151] This study found a large improvement in adherence among individuals who had had no prescription drug coverage before 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.

All five policy-level studies found statistically significant between-group differences in adherence to medications used to treat cardiovascular conditions, favoring the group that had out-of-pocket expenses reduced. However, we find these differences somewhat difficult to interpret because medication adherence decreased over time in all groups in two of the studies that used cohort designs. Nonetheless, the magnitude of effects observed in the cohort studies were similar to those reported in the RCT.[153] Therefore, we concluded that evidence of moderate strength indicates 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 (Table 77).

Table 77. Summary of evidence for policy-level interventions (KQ 2)

Clinical Condition	Intervention	Comparator	Number of Studies	Medication Adherence	Other Outcomes
Cardiovascular disease[149,153] Diabetes [149,151,152]	Improved prescription drug coverage[a]	Unchanged prescription drug coverage	5	Benefit: moderate SOE	Insufficient SOE
Cardiovascular disease[149,153] Diabetes [149,151,152]	Improved prescription drug coverage[a]	Unchanged prescription drug coverage	3	Benefit: moderate SOE	No evidence
Inhaled corticosteroids[b149]	Reduced medication copay	Unchanged medication copay	1	Insufficient SOE	No evidence

[a]Includes all policy-level interventions that reduced patient out-of-pocket expenses for prescription drugs.
[b]Inhaled corticosteroids are usually used to treat reactive airway disease conditions such as asthma and chronic obstructive pulmonary disease.
Abbreviation: SOE = strength of evidence.

Three policy-level studies found statistically significant between-group differences in adherence to medications used to treat diabetes, favoring the group that had out-of-pocket expenses reduced. As above, we find these differences somewhat difficult to interpret because all of these studies used cohort designs and medication adherence decreased over time in all groups in two of the studies. Nonetheless, the magnitude of effects observed in these two studies were similar to those in the Medicare Part D study among individuals who had had some prescription drug coverage before Medicare Part D but whose out-of-pocket medication expenses following its implementation dropped.[151] Therefore, we concluded that evidence of moderate strength indicates that policy-level interventions that reduce patient out-of-pocket expenses can have a beneficial effect on adherence to medications used to treat diabetes (Table 77).

One study found no effect of a policy-level intervention on adherence to inhaled corticosteroids, usually used to treat reactive airway disease conditions. Therefore, we concluded that evidence is insufficient to draw conclusions for the effectiveness of policy-level interventions in this clinical area (Table 77).

One study examined the effect of policy-level interventions on clinical outcomes.[153] This study found a 14 percent reduction in the rate of first vascular events following hospital discharge for a myocardial infarction. The same study found a 26 percent reduction in total patient spending, but no change in total insurer paying. We concluded that evidence is insufficient to draw conclusions regarding the effects of policy-level interventions on clinical and economic outcomes (Table 77).

Key Question 3a. Characteristics of Medication Adherence

Overall, the extreme heterogeneity of terminology used to describe medication adherence interventions in the studies reviewed hindered our ability to compare effects of different features of the interventions across studies and across diseases. In addition, the diversity of the interventions themselves made identification of "intervention type" clusters challenging.

Most, but not all, studies provided information (although not in a standardized manner) about six key intervention characteristics: 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 more than 50 percent of the interventions aimed at various combinations 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 these six key features, we identified some general patterns of combinations of the six features. For example, interventions varied in the number of contacts they entailed from 1 to 30, but those with more contacts tended to involve telephone contact. Similarly, certain intervention components, such as facilitation and knowledge-based components affecting the delivery of medical information, were commonly used across most interventions. In contrast, 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 programs than among either pharmacist- or physician-delivered interventions. The specific components of the interventions were the least well-characterized aspect of this literature, although often these components were the features that most meaningfully distinguished the interventions from one another. 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 with a usual-care control arm. Very 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. A longstanding debate exists about the advantages and disadvantages of testing multicomponent interventions, which may increase the likelihood of having an impact versus those of testing each component in isolation to understand its individual effects. Researchers may first combine approaches to document an effect and in later studies "peel away the layers of the onion" to isolate relative effects of separate components. The paucity of this second type of study design may reflect the state of the field. As studies increasingly demonstrate efficacious combination interventions, in the future we may see more studies that attempt to isolate effects of intervention features. Among the four studies that did conduct this kind of comparison, each compared *different* aspects of *different* interventions.

As a result, we could not pool data across even these four studies. One demonstrated that shared decisionmaking (in which nonphysician clinicians and patients negotiated a treatment regimen that accommodated patient goals and preferences) had a greater effect on adherence to asthma medications than did a clinical decision-making approach (in which the physician prescribed the treatment without specifically eliciting patient goals or preferences). Both approaches were more efficacious than usual care. The effects of shared decisionmaking on adherence lasted up to 2 years, whereas those attributed to clinical decisionmaking had attenuated at that point. Another study, conducted among patients with heart failure, directly compared two different delivery modes of the same information (telephone vs. videophone). This study found no difference between the two delivery modes regarding improvement in adherence, but both were superior to usual care. Another study directly compared the agent of delivery (physician vs. research staff) using the same mode (face-to-face contact) to deliver a decision aid among patients with diabetes to try to help them decide whether to take statins to lower their risk of cardiovascular disease. Patients who were given the decision aid had better adherence than those receiving usual care, regardless of who delivered the aid.

Thus, we conclude that mode of delivery was an important feature only in certain settings. However, incorporation of patient preferences through shared decisionmaking about treatment seems more efficacious at improving and sustaining improvement in asthma medication

adherence than traditional clinical decisionmaking that does not take into account patient preferences in selecting a recommended treatment. Shared decisionmaking appeared to improve pulmonary function tests when compared with clinical decisionmaking but this approach did not improve quality of life or health care utilization; we rated this evidence as having low strength (Table 78).

Key Question 4. Outcomes for Vulnerable Populations

We searched for evidence on a broad set of vulnerable populations. For certain vulnerable subgroups—specifically for patients with major depression, severe depression, or depression and coexisting hypertension; Black patients with depression and coexisting diabetes; elderly patients with diabetes, hyperlipidemia, heart failure, or hypertension—we determined that interventions with a positive impact on medication adherence had only low strength of evidence. Evidence was insufficient about benefit to adherence of interventions dealing with patients who had depression with coexisting HIV, patients who had diabetes and depression (except for African-American patients with diabetes and depression), patients with diabetes and hypertension, and patients from rural communities. 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 patients and 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 resulted in any unintended negative 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 great that we determined that the evidence was insufficient to reach definitive conclusions.

Table 78. 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[127]	Shared decisionmaking	Clinician decisionmaking	1	Benefit: low SOE	No evidence	Benefit: low SOE	Insufficient	No benefit: Low SOE	No benefit: Low SOE
Heart failure[115]	Telephone reminders	Video reminders	1	Insufficient	No evidence	No evidence	No evidence	No evidence	No evidence
Diabetes[93]	Decision aids delivered by clinician	Decision aids delivered by research staff	1	Insufficient	No evidence	No evidence	No evidence	No evidence	No evidence
Multiple chronic conditions[103]	Nurse case management with telemonitoring and high-intensity education	Nurse case management with telemonitoring and low-intensity education	1	Insufficient	No evidence	Not applicable	No evidence	No evidence	No evidence

Abbreviation: SOE = strength of evidence.

Findings in Relationship to What Is Already Known

This comparative effectiveness review contributes to the sizeable literature about medication adherence in several ways. A Cochrane review in 2008[28] of studies through 2007, demonstrated that medication adherence interventions can have moderate effects on medication adherence and health outcomes for several common chronic and acute medical conditions. Our review includes studies from 1994 through the present (2011)."In addition, patients' observations of medical regimens for infectious diseases can differ from practices by patients with chronic illnesses. Because several reviews had been conducted on interventions to improve HIV medication adherence,[80,157] we excluded studies on patients with HIV and other infectious. We also exclude studies of acute conditions to improve the ability to potentially pool findings-adherence to short-term, acute conditions is different than that for chronic medications; the Cochrane review included these. Hence, we are unable to comment on adherence interventions for those particular ailments.

We, like the Cochrane review, excluded substance abuse interventions also to improve ability to pool findings potentially since the involvement of physical and psychological addiction would make adherence to these treatments different than that of other treatment. We also excluded studies of adherence to medications for severe psychosis because these conditions require specific approaches that would not likely apply in other diseases.

Finally, the Cochrane review included only adherence studies that also assessed health outcomes. To broaden understanding of the impact of interventions on adherence, we included adherence intervention trials even if they did not assess other health outcomes. This decision likely expanded the variety of medication interventions included in this comparative effectiveness review. On the other hand, it is possible that while statistical significance for improved medication adherence was not seen in some studies, this may still translate into improvement of clinical outcomes. Decisionmakers should consider this possibility when designing programs to improve adherence in their particular organizations.

We included studies that assessed the effects of policy-level interventions, although these changes are relevant chiefly to the United States. Our findings are fairly consistent with studies conducted of HIV adherence. Rueda and colleagues conducted a Cochrane Database review of 19 patient education and support interventions of 2,159 patients and found that methods were too heterogeneous to conduct a meta-analysis. They identified a broad range of intervention types, including cognitive behavioral therapy, motivational interviewing, medication management strategies, and interventions indirectly targeting adherence, such as programs directed to reduce risky sexual behaviors. Ten of the 19 studies indicated the invention was beneficial to adherence. Unlike our review, this HIV review showed some characteristics of interventions associated with improved adherence outcomes: targeting practical medication management skills, administering interventions to individuals rather than groups, and delivering over at least 12 weeks had a greater impact on adherence with improved adherence outcomes.[157] In contrast, a meta-analysis by Simoni and colleagues showed that when data were pooled, participants in the intervention arms were more likely than controls to attain 95 percent adherence (OR = 1.50, 95% CI, 1.16 to 1.94), and this effect was stronger in studies that used recall periods of at least 2 weeks. They could not identify differences based on intervention features and concluded, as we have, that more research to identify the most efficacious intervention components is needed.[80] Unlike other reviews, we analyzed intervention effects in relation to intervention type, to identify those programs with the strongest evidence. This information has the potential to offer actionable

information for policymakers and practitioners working within clinical domains. The 20 intervention clusters we identified, which included categories like case management, coordinated care, shared decisionmaking, education with social support, and so forth, as listed in Table 74 provide a starting framework by which practitioners and researchers may develop, test, and report their adherence programs more explicitly and consistently.

In addition to identifying empirically derived clusters, this review has characterized interventions targeting medication adherence based on six intervention features: target, agent, mode, intensity, duration, and components. The information about variations in these six features has not been reported previously and provides a second approach to reporting adherence programs in a more standardized manner. Ultimately, if studies used this framework more consistently, future reviews might be able more easily to pool data and pursue syntheses that could provide more robust data and more precise estimates of effects. As with other active areas of research, ongoing trials have the potential to shift the weight of evidence: this systematic review will need to be updated frequently.

Finally, unlike other reviews of RCTs testing interventions for medication adherence, ours is the first attempt to understand the moderating effects of population characteristics on intervention effects. We did this by analyzing data from included studies that pertained to vulnerable populations (described in KQ 4 above). The paucity of evidence in this area highlights the need for future studies to include vulnerable populations.

Applicability

The interventions analyzed in this review were not highly selective; rather, they ranged from relatively minimalist to complex and intense, although evidence often came from small studies. Neither were these studies limited to narrow or unrepresentative disorders or disease severity; rather, they reflected studies done across a substantial variety of chronic conditions affecting adults. Thus, in one sense the evidence from this comparative effectiveness review might be regarded as relatively applicable across numerous different options for health care providers to pursue for their adult patients with major chronic diseases or multiple chronic conditions. Our findings are not generalizable to children or young adolescents because of our inclusion criteria.

As noted, many of our findings came from single, often small or short-term, trials, some with important questions about risk of bias. Findings from this diversity clinical conditions and interventions have not yet been replicated in trials in larger patient populations, in groups drawn from different settings and with different sociodemographic characteristics, or in investigations with longer observation and followup periods. These gaps in the evidence base constrain somewhat the applicability of our results.

Another limitation to the applicability of this evidence comes from the complexity of multicomponent interventions. Studies did not generally provide information on how researchers identified the separate active components in their interventions or how they had operationalized those components; generally, these complex programs lacked detailed instructions and users' manuals by which other groups might try to replicate the original research.

Finally, the degree to which these interventions require fidelity to protocol when being implemented in other settings or through different study designs (e.g., nonexperimental studies) is unclear. The need for fidelity to protocol, or the allowable, appropriate adjustments for other patient populations (e.g., different illnesses; different sociodemographic characteristics) is likely a matter of some debate. These questions place some limits on the wide applicability of the evidence reported here.

Implications for Clinical and Policy Decisionmaking

We found evidence of effective interventions to improve medication adherence for many chronic conditions. These analyses suggest that patients' adherence to chronic-disease medications can be improved through programs targeting patients, providers, health systems, or policy. They demonstrated that a broad range of approaches can work.

Adherence is typically the result of a combination of patient, provider, and policy factors. Indeed, most of the 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, no single "silver bullet" exists for medication adherence.

We found the strongest evidence for enhancing adherence with reduced copays across clinical conditions, self-management of asthma (for short-term outcomes), and collaborative care or case management for depression. Within clinical conditions, we found the strongest evidence with depression case management for depression symptom improvement and pharmacist-led hypertension approaches for systolic blood pressure improvement. We found consistent evidence or evidence from more than one clinical area supporting medication adherence interventions such as education, reminders, and pharmacist-led multicomponent interventions.

Clinicians and policymakers should keep in mind that we found very little evidence of any relationship between medication adherence and adverse events, although what we found suggests that improving adherence did not increase the incidence of adverse events. However, many of the conditions studied did not involve medications typically associated with very severe common side effects. This review is the first we are aware of that systematically reviewed information on adverse events. It thus provides information that should be confirmed in future studies and reviews.

The lack of studies evaluating potential mechanisms that link improved adherence with other health-related or health services outcomes somewhat constrains policymakers' and clinicians' options. We did not find evidence of studies among patients with chronic illnesses who tend to have more intermittent disease trajectories, such as certain types of arthritis, diverticulitis, and other gastrointestinal conditions. In particular, decisionmakers should exercise caution in trying to use any a la carte approach to implementing components of complex interventions to enhance patients' medication adherence. We do not think that sufficient information is yet available to guide choices among the considerable array of program components, especially to pick and choose only some parts of multicomponent approaches. Therefore, future studies must 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. Meanwhile, however,if studies have not been done in their specific clinical patient population, clinicians and health system administrators may want to give more thought to how they might be able to extrapolate existing results to their specific patient populations—that is take apparently successful programs and apply them to groups with diagnoses and other characteristics similar to those in the successful program. For example, interventions similar to those that were successful at improving adherence to medication for hypertension and hyperlipidemia may help in other settings in which the illness is asymptomatic and medication is taken primarily to prevent long-term complications.

Poor medication adherence is known to result in large downstream health care costs. An important finding for policymakers contemplating changes in health policy is our assessment of moderate-strength evidence, from five consistent studies, that reducing patients' out-of-pocket costs or improving prescription drug coverage 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 limit the applicability of this review, as discussed above. We did not review the evidence on populations with human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), mania, bipolar disorder, or substance abuse. We excluded studies among patients with HIV/AIDS because existing comprehensive reviews of these interventions had been conducted recently. We also excluded studies of acute conditions, severe mental illness and substance abuse to improve our ability to potentially pool findings since adherence to short-term, acute conditions, those involving addictions or cognitive limitations are different than that for chronic medications. However, interventions for these excluded clinical conditions may have applicability to the conditions that we included in our review. We limited this review to adults and cannot, therefore, address important adherence concerns for children and adolescents with chronic conditions such as type 2 diabetes. Another limitation is geographic location: we excluded non-English and non-U.S. studies. This criterion may well have decreased the pool of eligible studies we might have examined, but their applicability to the United States is unclear. Our approach to categorizing interventions for KQ 1 relied essentially on the short descriptions in published manuscripts; their similarities or differences substituted for any overarching taxonomy, as none that we considered seemed fit our purpose. Thus, we have introduced intervention labels that, admittedly, do not fully describe or account for heterogeneity within and across clinical conditions or patient populations. This approach limits our ability to make definitive statements about the effectiveness of interventions across clinical areas; we believe the clusters and categorizations we used are useful heuristics, but they may be regarded more as hypothesis generating than reflecting settled principles of classification. Finally, our pool of included interventions is limited to those that were designed specifically to address medication adherence as a primary or secondary outcome. We did not include clinical trials of drugs that considered adherence as a component of safety and efficacy; as a result, we do not address the effectiveness of specific drug formulations that may improve adherence by limiting adverse effects.

Limitations of the Evidence Base

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 our ability to pool results from studies. If investigators could use more standardized, objective adherence outcomes in future research, their results might be more easily analyzed and interpreted 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 we could safely draw about the efficacy of specific intervention features. Although 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.

Most trials were not placed in a larger context of improving the quality of health care delivered; only a minority examined issues such as quality of life and patient-reported outcomes or patient satisfaction. This limitation interacts with the issues noted above about understanding the effectiveness of these programs, not simply their efficacy, which is especially important for providing information suitable for broadly based clinical and policy decisionmaking. At a minimum, using guidelines from the Standards for Quality Improvement Reporting Excellence (SQUIRE) group (http://squire-statement.org/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.[158]

Finally, although many studies did assess some health outcomes, these often were not reported by patients themselves, and many were relatively short term (at least in the context of lifelong chronic ailments). Including long-term health outcomes and mounting efforts to solicit information directly from patients in future trials or observational studies of adherence would enhance the nation's capacity to assess the overall significance of adherence interventions. While the minimum length of followup indicated may vary by condition, for lifelong chronic ailments, medication adherence often decays over at least the first year. Hence, studies that follow patients longer than one year could provide information about adherence levels once they have reached a plateau. Collecting information about costs will be crucial, because no health systems or facilities can afford to try all approaches across the diverse patient populations they serve. Economic information is essential in and of itself, but it will facilitate cost-effectiveness analyses of such interventions.

Research Gaps

We found numerous gaps in the literature, described in the sections below. The following key research gaps have emerged across key questions and clinical conditions:

- Some clinical areas revealed a paucity of evidence. Among the conditions that we reviewed, we found limited evidence for myocardial infarction, multiple sclerosis, glaucoma, and multiple chronic conditions.
- The evidence focuses on clinical conditions with relatively stable or increasing levels of morbidity; effective adherence interventions for these conditions may not be effective for conditions with episodic symptomatology.
- Information on subgroup analysis was limited; despite our relatively wide search for evidence on vulnerable populations, we found very little evidence.
- Information on adverse events, health outcomes, quality of life, costs, and healthcare utilization was limited.
- Information on long-term outcomes was limited.
- Information was limited or not available on the effectiveness of components or mechanisms of action of complex or practice-driven interventions.
- The wide heterogeneity of measures and outcomes made synthesis challenging. Future efforts to pool evidence would benefit from the use of standard and valid measures.

Key Question 1. Patient, Provider, and Systems Interventions

Diabetes

The body of evidence for diabetes was relatively sparse and provided low strength of evidence. 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 have 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. Studies that seek to advance understanding whether the impact of interventions for diabetes medications varies for different subgroups (such as groups with low health literacy, very poorly controlled diabetes, or other vulnerable populations) may be beneficial. This analysis 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 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.

Cardiovascular Disease 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 three heart failure trials that found improved medication adherence also reported additional outcomes, including health care utilization in two of them. Among the 17 trials conducted in patients with hypertension, seven found improved adherence or persistence and six of the seven reported systolic and diastolic blood pressure outcomes, but only two reported health care utilization outcomes. Among the nine trials in hyperlipidemia, four found improvements in either medication adherence or persistence; only two of the four 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, among the trials with improved adherence, few in the hypertension group and none 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. Studies need to evaluate clinical outcomes in addition to adherence outcomes for patients after myocardial infarction. We only included trials in the myocardial infarction section that aimed to improve adherence to medications to treat myocardial infarction. We discussed trials that aimed to improve adherence to medications to treat diseases that are risk factors for myocardial infarction (hypertension, diabetes, hyperlipidemia) or that may have been related to a myocardial infarction (heart failure) elsewhere as independent clinical categories.

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 or hyperlipidemia trials. Future research could enhance our understanding of how medication adherence interventions could affect these outcomes as well.

Asthma

Among included asthma trials, we found that no long-term outcomes were reported for short-term interventions; this finding was true for many of the trials included in this review for other clinical conditions as well. For asthma, interventions lasting 4 to 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 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.

Depression

Seven out of 11 depression interventions reported improvements in medication adherence, with seven of these trials reporting on health outcomes. However, these trials provided 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 to 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.

Other Chronic Conditions

For interventions in the areas of unspecified or multiple chronic conditions, glaucoma, multiple sclerosis, 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. In 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 multiple sclerosis, 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 three 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 five studies investigating policy-level interventions yielded important evidence that reducing patient out-of-pocket expenses for prescription medications can improve medication adherence. However, only one of these studies examined the effect of these policy changes on any patient-centered or health-related outcomes. Thus, future studies on policy interventions should focus more on how such interventions can improve actual management of these chronic conditions. Of particular interest are measures of blood pressure, lipid levels, and other intermediate outcomes and biomarkers; long-term health outcomes, such as rates of myocardial infarctions or strokes and measures of patient-reported quality of life and health status; and use of health care services.

In addition, none of the studies examined whether the impact of these interventions varied across different population subgroups. For example, policy-level interventions designed to reduce out-of-pocket costs most likely have the greatest effect among individuals with limited incomes and those using several medications. This type of 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 clarify how policy-level interventions may change the trajectory of adherence over time, beginning at the initiation of therapy.

Key Question 3. Intervention Characteristics

We identified six main properties of medication adherence interventions, which we called their target, agent, mode, intensity, duration, and components. Our capacity to describe fully the variation in these features was limited in two ways: by the sheer diversity of the programs and the measures used to assess outcomes, and by language that the various investigator teams used to describe their interventions' features.

We suggest that future studies in this field adopt a standardized manner for describing interventions. It should include a clear report of the intended targets of the intervention, all agents, and modes of delivery using the categories we have identified here. We believe that investigators would find describing the intensity and duration of all interventions in a similarly standardized manner relatively simple; such descriptions should include 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 almost 15 years ago[159] enabled systematic reviewers to do a much better job than previously of comparing and pooling clinical trial results, such a simple step as standardizing reporting descriptions of interventions might similarly enhance capacity to understand the effects of different aspects of these intervention. Similarly, researchers in this field might consider using deBruin's taxonomy,[74] which consists of specific definitions of each of several components to report their intervention components. Others could then have a better basis for cataloguing these features as a first step in comparing their utility across studies.

Finally, we found only four studies that directly compared specific components or approaches of interventions. More standardized descriptions of interventions, as advocated above, will enhance the capacity of systematic reviewers to pool data across studies and efficiently compare effects of specific features. Nevertheless, as we gain insight into what

features are most critical, more studies will be needed that directly compare elements of interventions. 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. Observational studies (not included in this review) may generate hypotheses regarding the mechanisms by which complex or practice-driven interventions work.

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.

Key Question 4. Vulnerable Populations

We encourage health systems, insurers, and others to mount studies for the considerable range of population groups that we had intended to examine but on whom we found little to no literature. These include most racial and ethnic minorities, although African-American populations were reasonably well covered in this evidence base. People with a variety of characteristics putting them at risk of disparities in health care and health outcomes warrant more attention, especially those for whom English is a second language, those with low levels of literacy or health literacy, and those of low income or poor or no health insurance. As to the latter, more studies of children covered by state Medicaid programs or the Child Health Insurance Program might be warranted.

We believe that the evidence base for mainstream patient populations with common chronic conditions points toward a variety of medication adherence programs suitable for these groups. Other clinical populations facing substantial health challenges remain understudied. These include persons with dual mental health diagnoses (e.g., depression and a substance abuse problem) and persons with complex medical histories (e.g., multiple chronic conditions).

Key Question 5. Adverse Events

Interventions designed to improve medication adherence did not, in our very small evidence base, appear to increase adverse events, harms, or unintended consequences. However, routine tracking of adverse events related to attempts to improve adherence has apparently not received much (certainly not sufficient) attention in the literature. The fact that all pharmacotherapies for chronic conditions pose some risks to at least some patients—and in some cases (such as depression) the choice of drug may turn on the adverse events profile, not efficacy or effectiveness data—makes clear the need to improve and expand evaluation of harms, particularly over the long run. We advocate that investigators build into their trials or effectiveness studies more routine measurement of possible harms or unintended effects, in addition to benefits of greater medication adherence per se.

Conclusions

Despite the heterogeneity of adherence measurement, interventions tested, and characterization of interventions, we found the most consistent evidence of improvement in medication adherence for policy-level interventions to reduce out-of-pocket expenses or improve prescription drug coverage, case management, and educational interventions across clinical conditions. Within clinical conditions, we found the strongest support for self-management of

medications for short-term improvement in adherence for asthma patients; collaborative care or case management programs for short-term improvement in adherence and symptom improvement for patients taking depression medications; and pharmacist-led approaches in hypertensive patients for improvement of systolic blood pressure.

We found low strength of evidence for many other interventions; these diverse groups of approaches offer promise but require more research to establish their value (or lack of it). Far less evidence was available to show whether most of these interventions improved patients' health outcomes, given better adherence to their medication regimens. Several reviews that researchers have conducted over the past two decades—now complemented by our comparative effectiveness review—confirm that medication adherence can be improved via formal programs of various sorts. 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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Appendix A. Search Strategies

Preliminary searches and topic scoping occurred from January 2011 to March 2011. Update searches occurred in November and December 2011. The search strategies below are the final search strategies for randomized controlled trials (RCTs), policy-related publications, and Cochrane reviews.

PubMed Main RCT Search

Main RCT search done April 21, 2011; 2677 results.

Search	Queries	Result
#1	Search "Patient Compliance"[Mesh]	42003
#2	Search "Patient Compliance"[ti]	714
#3	Search adherence[tiab]	48121
#4	Search "Medication Adherence"[Mesh]	2291
#5	Search "medication compliance"[tiab]	882
#6	Search "medication persistence"[tiab]	42
#7	Search "Medication Reconciliation"[Mesh]	27
#8	Search #1 or #2 or #3 or #4 or #5 or #6 or #7	81627
#9	Search "Intervention Studies"[Mesh]	4636
#10	Search intervention[tiab] OR interventions[tiab]	385603
#11	Search "control group"[tiab] OR "control groups"[tiab] OR "treatment group"[tiab] OR "treatment groups"[tiab]	265702
#12	Search #8 and #9	311
#13	Search #8 and #10	10363
#14	Search #8 and #11	3283
#15	Search #12 or #13 or #14	12246
#16	Search #15 Limits: Humans, English, All Adult: 19+ years, Publication Date from 1994	6150
#17	Search #16 Limits: Editorial, Letter, Comment, News	22
#18	Search #16 NOT #17	6128
#19	Search "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH]	381238
#20	Search #18 and #19	2677

PubMed Main RCT Search Update

This search was identical to the April 21, 2011 main RCT search described above. Date range: 1994-2011. 225 results (0 duplicates) were unique and imported to the database.

Search	Queries	Result
#1	Search "Patient Compliance"[Mesh]	43881
#2	Search "Patient Compliance"[ti]	727
#3	Search adherence[tiab]	50921
#4	Search "Medication Adherence"[Mesh]	3036
#5	Search "medication compliance"[tiab]	913
#6	Search "medication persistence"[tiab]	48
#7	Search "Medication Reconciliation"[Mesh]	70
#8	Search #1 or #2 or #3 or #4 or #5 or #6 or #7	85526
#9	Search "Intervention Studies"[Mesh]	4913
#10	Search intervention[tiab] OR interventions[tiab]	407959
#11	Search "control group"[tiab] OR "control groups"[tiab] OR "treatment group"[tiab] OR "treatment groups"[tiab]	277165
#12	Search #8 and #9	334
#13	Search #8 and #10	11176
#14	Search #8 and #11	3465
#15	Search #12 or #13 or #14	13140
#16	Search #15 Limits: Humans, English, All Adult: 19+ years, Publication Date from 1994	6670
#17	Search #16 Limits: Editorial, Letter, Comment, News	22
#18	Search #16 NOT #17	6648
#19	Search "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH]	394126
#20	Search #18 and #19	2882
#23	Search 2010/10:2011/11[edat]	962001
#24	Search #20 and #23	225

PubMed Policy Search

Policy search done April 21, 2011 includes terms suggested by Technical Expert Panel (TEP) and alternate indications for interventions; 1064 results. 371 are unique and were imported to the database.

Search	Most Recent Queries	Result
#1	Search "Patient Compliance"[Mesh]	42003
#2	Search "Patient Compliance"[ti]	714
#3	Search adherence[tiab]	48121
#4	Search "Medication Adherence"[Mesh]	2291
#5	Search "medication compliance"[tiab]	882
#6	Search "medication persistence"[tiab]	42
#7	Search "Medication Reconciliation"[Mesh]	27
#8	Search #1 or #2 or #3 or #4 or #5 or #6 or #7	81627
#9	Search "Intervention Studies"[Mesh]	4636
#10	Search intervention[tiab] OR interventions[tiab]	385603
#11	Search "control group"[tiab] OR "control groups"[tiab] OR "treatment group"[tiab] OR "treatment groups"[tiab]	265702
#12	Search #8 and #9	311
#13	Search #8 and #10	10363
#14	Search #8 and #11	3283
#15	Search #12 or #13 or #14	12246
#16	Search #15 Limits: Humans, English, All Adult: 19+ years, Publication Date from 1994	6150
#17	Search #16 Limits: Editorial, Letter, Comment, News	22
#18	Search #16 NOT #17	6128
#19	Search "Infection Control"[Mesh]	44446
#20	Search #18 and #19	25
#21	Search "Policy Making"[Mesh]	15482
#22	Search #18 and #21	1
#23	Search "Public Policy"[Mesh]	92346
#24	Search #18 and #23	32
#25	Search "State Health Planning and Development Agencies"[Mesh]	780
#26	Search #18 and #25	0
#27	Search "Insurance Claim Review"[Mesh]	3437
#28	Search #18 and #27	20
#29	Search "Medicare Part D"[Mesh]	568
#30	Search #18 and #29	12
#31	Search "Health Services Accessibility"[Mesh]	69354
#32	Search #18 and #31	80
#33	Search "Health Policy"[Mesh]	67320
#34	Search #18 and #33	32
#35	Search "Formularies as Topic"[Mesh]	2537
#36	Search #18 and #35	6
#37	Search "Gatekeeping"[Mesh]	453
#38	Search #18 and #37	0
#39	Search "Community Pharmacy Services"[Mesh]	2123
#40	Search #18 and #39	61
#41	Search "Medication Therapy Management"[Mesh]	270
#42	Search #18 and #41	9
#43	Search "Cost-Sharing"[Mesh]	3121
#45	Search "cost sharing"	2144
#46	Search #43 or #45	3517
#47	Search #18 and #46	14
#48	Search "Health Benefit Plans, Employee"[Mesh]	9132
#49	Search #18 and #48	7
#50	Search "prior authorization"	216
#51	Search #18 and #50	0
#52	Search "Insurance, Pharmaceutical Services"[Mesh]	3675

Search	Most Recent Queries	Result
#53	Search #18 and #52	31
#54	Search "Prescription Drugs"[Mesh]	1151
#55	Search #18 and #54	8
#56	Search "Drug Costs"[Mesh]	10161
#57	Search #18 and #56	31
#58	Search "system-level"	1253
#59	Search #18 and #58	5
#60	Search "pharmaceutical care program" OR "pharmaceutical care programs"	44
#61	Search #18 and #60	13
#62	Search "Health Services Research"[Mesh]	99483
#63	Search #18 and #62	186
#64	Search "Medical Indigency"[Mesh]	3433
#65	Search #18 and #64	1
#66	Search "Program Development"[Mesh]	18203
#67	Search #18 and #66	54
#68	Search "medication possession ratio" OR "medication possession ratios" OR MPR	1928
#69	Search #18 and #68	39
#70	Search "Pharmacy Service, Hospital"[Mesh]	9015
#71	Search #18 and #70	24
#72	Search "prescribing pattern" OR "prescribing patterns"	1392
#73	Search #18 and #72	6
#74	Search "Medicaid"[Mesh]	16680
#75	Search #18 and #74	19
#76	Search "Treatment Refusal"[Mesh]	9644
#77	Search #18 and #76	123
#78	Search "Polypharmacy"[Mesh]	1523
#79	Search #18 and #78	19
#80	Search "Drug Combinations"[Mesh]	52143
#81	Search #18 and #80	34
#82	Search "Drug Packaging"[Mesh]	8342
#83	Search #18 and #82	35
#84	Search "Disease Management"[Mesh]	7390
#85	Search #18 and #84	64
#86	Search "Drug Administration Schedule"[Mesh]	75117
#87	Search #18 and #86	188
#88	Search "Managed Care Programs"[Mesh]	37687
#89	Search #18 and #88	91
#90	Search "Health Maintenance Organizations/organization and administration"[Mesh]	9938
#91	Search #18 and #90	23
#92	Search "Primary Health Care/economics"[Mesh]	3422
#93	Search #18 and #92	18
#94	Search "Primary Health Care/organization and administration"[Mesh]	25797
#95	Search #18 and #94	117
#96	Search #20 or #22 or #24 or #26 or #28 or #30 or #32 or #34 or #36 or #38 or #40 or #42 or #47 or #49 or #51 or #53 or #55 or #57 or #59 or #61 or #63 or #65 or #67 or #69 or #71 or #73 or #75 or #77 or #79 or #81 or #83 or #85 or #87 or #89 or #91 or #93 or #95	1064

November 14, 2011. PubMed Policy Search Update

This search was identical to the April 21, 2011 policy search described above. Date range: 1994-2011. 87 results (51 duplicates), 36 of which were unique and imported to the database.

Search	Most Recent Queries	Result
#1	Search "Patient Compliance"[Mesh]	43881
#2	Search "Patient Compliance"[ti]	727
#3	Search adherence[tiab]	50921
#4	Search "Medication Adherence"[Mesh]	3036
#5	Search "medication compliance"[tiab]	913
#6	Search "medication persistence"[tiab]	48
#7	Search "Medication Reconciliation"[Mesh]	70
#8	Search #1 or #2 or #3 or #4 or #5 or #6 or #7	85526
#9	Search "Intervention Studies"[Mesh]	4913
#10	Search intervention[tiab] OR interventions[tiab]	407959
#11	Search "control group"[tiab] OR "control groups"[tiab] OR "treatment group"[tiab] OR "treatment groups"[tiab]	277165
#12	Search #8 and #9	334
#13	Search #8 and #10	11176
#14	Search #8 and #11	3465
#15	Search #12 or #13 or #14	13140
#16	Search #15 Limits: Humans, English, All Adult: 19+ years, Publication Date from 1994	6670
#17	Search #16 Limits: Editorial, Letter, Comment, News	22
#18	Search #16 NOT #17	6648
#19	Search "Infection Control"[Mesh]	45461
#20	Search #18 and #19	29
#21	Search "Policy Making"[Mesh]	16027
#22	Search #18 and #21	2
#23	Search "Public Policy"[Mesh]	95699
#24	Search #18 and #23	34
#25	Search "State Health Planning and Development Agencies"[Mesh]	785
#26	Search #18 and #25	0
#27	Search "Insurance Claim Review"[Mesh]	3634
#28	Search #18 and #27	22
#29	Search "Medicare Part D"[Mesh]	657
#30	Search #18 and #29	16
#31	Search "Health Services Accessibility"[Mesh]	71702
#32	Search #18 and #31	91
#33	Search "Health Policy"[Mesh]	70065
#34	Search #18 and #33	34
#35	Search "Formularies as Topic"[Mesh]	2566
#36	Search #18 and #35	6
#37	Search "Gatekeeping"[Mesh]	465
#38	Search #18 and #37	0
#39	Search "Community Pharmacy Services"[Mesh]	2224
#40	Search #18 and #39	65
#41	Search "Medication Therapy Management"[Mesh]	323
#42	Search #18 and #41	12
#43	Search "Cost-Sharing"[Mesh]	3200
#44	Search "cost sharing"	2202
#45	Search #43 or #44	3607
#46	Search #18 and #45	17
#47	Search "Health Benefit Plans, Employee"[Mesh]	9199
#48	Search #18 and #47	7
#49	Search "prior authorization"	221
#50	Search #18 and #49	0
#51	Search "Insurance, Pharmaceutical Services"[Mesh]	3821
#52	Search #18 and #51	38

Search	Most Recent Queries	Result
#53	Search "Prescription Drugs"[Mesh]	1438
#54	Search #18 and #53	10
#55	Search "Drug Costs"[Mesh]	10478
#56	Search #18 and #55	33
#57	Search "system-level"	1385
#58	Search #18 and #57	6
#59	Search "pharmaceutical care program" OR "pharmaceutical care programs"	46
#60	Search #18 and #59	13
#61	Search "Health Services Research"[Mesh]	103503
#62	Search #18 and #61	199
#63	Search "Medical Indigency"[Mesh]	3439
#64	Search #18 and #63	1
#65	Search "Program Development"[Mesh]	19001
#66	Search #18 and #65	60
#67	Search "medication possession ratio" OR "medication possession ratios" OR MPR	2049
#68	Search #18 and #67	44
#69	Search "Pharmacy Service, Hospital"[Mesh]	9149
#70	Search #18 and #69	26
#71	Search "prescribing pattern" OR "prescribing patterns"	1461
#72	Search #18 and #71	6
#73	Search "Medicaid"[Mesh]	17092
#74	Search #18 and #73	19
#75	Search "Treatment Refusal"[Mesh]	9798
#76	Search #18 and #75	125
#77	Search "Polypharmacy"[Mesh]	1667
#78	Search #18 and #77	22
#79	Search "Drug Combinations"[Mesh]	53239
#80	Search #18 and #79	38
#81	Search "Drug Packaging"[Mesh]	8514
#82	Search #18 and #81	38
#83	Search "Disease Management"[Mesh]	7709
#84	Search #18 and #83	65
#85	Search "Drug Administration Schedule"[Mesh]	76914
#86	Search #18 and #85	196
#87	Search "Managed Care Programs"[Mesh]	37866
#88	Search #18 and #87	93
#89	Search "Health Maintenance Organizations/organization and administration"[Mesh]	9960
#90	Search #18 and #89	23
#91	Search "Primary Health Care/economics"[Mesh]	3579
#92	Search #18 and #91	18
#93	Search "Primary Health Care/organization and administration"[Mesh]	26856
#94	Search #18 and #93	127
#96	Search #20 or #22 or #24 or #26 or #28 or #30 or #32 or #34 or #36 or #38 or #40 or #42 or #46 or #48 or #50 or #52 or #54 or #56 or #58 or #60 or #62 or #64 or #66 or #68 or #70 or #72 or #74 or #76 or #78 or #80 or #82 or #84 or #86 or #88 or #90 or #92 or #94	1145
#97	Search **2010/10:2011/11[edat]**	962001
#98	Search #96 and #97	87

April 25, 2011. Wiley Interface of the Cochrane Library

This search covers both main RCT and policy searches, it is not limited to interventions or study types. Date range: 1994-2011. 5,810 results, 38 of which were Cochrane Reviews (1 duplicate), 149 were Other Reviews (0 duplicates), and 17 were technical assessments (0 duplicates); 203 records were imported to the database.

Search	Most Recent Queries	Result
#1	MeSH descriptor **Patient Compliance** explode all trees	7068
#2	"medication compliance":ti or "medication compliance":ab	251
#3	"medication persistence":ti or "medication persistence":ab	6
#4	"medication reconciliation":ti and "medication reconciliation":ab	3
#5	"patient compliance":ti	122
#6	(#1 OR #2 OR #3 OR #4 OR #5)	7258
#7	(#6), from 1994 to 2011	5810

December 8, 2011. Update Search for Wiley interface of the Cochrane Library

This search was identical to the April 25, 2011 main RCT search described above, except that it was limited to 2010-2011. Date range: 2010-2011. 764 results, 25 of which were Cochrane Reviews (18 duplicates), 5 were technical assessments (4 duplicates), and 27 were Other Reviews (7 duplicates); 28 records were imported to the database.

Search	Most Recent Queries	Result
#1	MeSH descriptor **Patient Compliance** explode all trees	7079
#2	"medication compliance":ti or "medication compliance":ab	254
#3	"medication persistence":ti or "medication persistence":ab	3
#4	"medication reconciliation":ti and "medication reconciliation":ab	3
#5	"patient compliance":ti	119
#6	(#1 OR #2 OR #3 OR #4 OR #5)	7270
#7	(#6), from 2010 to 2011	764

Appendix B. Abstract and Full- Text Forms

The following are lists of fields used in the abstract and full- text review forms. Please see the Evidence Tables (Appendix D) for fields used in the data abstraction forms.

Reviewers were asked to complete the following fields for screening abstracts for inclusion:

Reviewer
REF ID
Author
Year
Title
Abstract
Include
Exclude (check the box below and then check the box to the right that indicates your first reason for exclusion)
Wrong publication type (e.g. editorials, letters, non-systematic reviews, case-reports, case series)
Wrong country
Wrong Intervention
Wrong study design
Wrong population
No /wrong comparison
Wrong outcome
Wrong Setting
Other (please write in specific reason)
Comments: Please include a comment if you included an abstract, but did so do to a lack of clarity within the abstract. Explain why you think the FT will reveal that the study should be excluded.

Reviewers were asked to consider and complete the following fields when reviewing full texts for inclusion:

Reviewer
Ref ID
Authors
Year
Title
Include?
Exclude?
If Exclude, select most significant reason for exclusion from ordered list. (list of options is provided below) If Other, note reason in next column.
If Exclude Reason is Other, please explain
If Include, is medication adherence SOLELY self-reported? Y or N
If Include AND country is non-US, please write country name
If Include, KQ1a?

If Include for KQ1a: Did study improve Med Adh?
If study improved Med Adh AND KQ1a include: Include for KQ1b?
If Include, KQ2a?
If Include for KQ2a: Did study improve Med Adh?
If study improved Med Adh AND KQ2a include: Include for KQ2b?
If Include, KQ3?
If Include, KQ4?
If Include, KQ5?
If Pilot Study add citation
Other Comments

FT Exclude Reasons (choices provided in drop down list)

Intervention not Med Ad related
No Intervention
No Med Ad outcomes
Ineligible Population
Ineligible Study Design
Pilot Study (add citation)
Ineligible Setting
Ineligible Comparator
Sample Size < 40
Ineligible Publication Type
Other (add comment)

Appendix C. Excluded Studies

Studies excluded at the full text level.

The list below includes 637 studies excluded at the full text level for the following reasons:

X1: Intervention not related to medication adherence
X2: No intervention
X3: Non-US
X4: Infectious conditions, HIV-related, mental illness involving psychosis, sub abuse
X5: Ineligible study design
X6: Ineligible setting
X7: Ineligible comparator
X8: Sample size <40
X9: Ineligible publication type
X10: Pre-1994
X12: No medication adherence outcomes
X13: Ineligible population
X14: Ineligible systematic review

Studies excluded for high risk of bias (N = 24) are listed in Appendix E.

	Study Information	Exclusion Code
1	Implementation of treatment protocols in the Diabetes Control and Complications Trial. Diabetes Care. 1995 Mar;18(3):361-76.	X1
2	Testing combined pharmacotherapies and behavioral interventions for alcohol dependence (the COMBINE study): a pilot feasibility study. Alcohol Clin Exp Res. 2003 Jul;27(7):1123-31.	X13
3	Abrahams N, Jewkes R, Lombard C, Mathews S, Campbell J, Meel B. Impact of telephonic psycho-social support on adherence to post-exposure prophylaxis (PEP) after rape. AIDS Care. 2010 Oct;22(10):1173-81.	X3
4	Abraira C, Colwell JA, Nuttall FQ, Sawin CT, Nagel NJ, Comstock JP, et al. Veterans Affairs Cooperative Study on glycemic control and complications in type II diabetes (VA CSDM). Results of the feasibility trial. Veterans Affairs Cooperative Study in Type II Diabetes. Diabetes Care. 1995 Aug;18(8):1113-23.	X1
5	Adler DA, Bungay KM, Wilson IB, Pei Y, Supran S, Peckham E, et al. The impact of a pharmacist intervention on 6-month outcomes in depressed primary care patients. Gen Hosp Psychiatry. 2004 May-Jun;26(3):199-209.	X12
6	Akerblad AC, Bengtsson F, Ekselius L, von Knorring L. Effects of an educational compliance enhancement programme and therapeutic drug monitoring on treatment adherence in depressed patients managed by general practitioners. Int Clin Psychopharmacol. 2003 Nov;18(6):347-54.	X3
7	Al-aqeel S, Al-sabhan J. Strategies for improving adherence to antiepileptic drug treatment in patients with epilepsy. Cochrane Database of Systematic Reviews. 2011(1).	X14
8	Al-Eidan FA, McElnay JC, Scott MG, McConnell JB. Management of Helicobacter pylori eradication--the influence of structured counselling and follow-up. Br J Clin Pharmacol. 2002 Feb;53(2):163-71.	X3
9	Al-Rashed SA, Wright DJ, Roebuck N, Sunter W, Chrystyn H. The value of inpatient pharmaceutical counselling to elderly patients prior to discharge. Br J Clin Pharmacol. 2002 Dec;54(6):657-64.	X3
10	Altice FL, Maru DS, Bruce RD, Springer SA, Friedland GH. Superiority of directly administered antiretroviral therapy over self-administered therapy among HIV-infected drug users: a prospective, randomized, controlled trial. Clin Infect Dis. 2007 Sep 15;45(6):770-8.	X4
11	Altice FL, Mezger JA, Hodges J, Bruce RD, Marinovich A, Walton M, et al. Developing a directly administered antiretroviral therapy intervention for HIV-infected drug users: implications for program replication. Clin Infect Dis. 2004 Jun 1;38 Suppl 5:S376-87.	X4

	Study Information	Exclusion Code
12	Amado Guirado E, Pujol Ribera E, Pacheco Huergo V, Borras JM. Knowledge and adherence to antihypertensive therapy in primary care: results of a randomized trial. Gac Sanit. 2011 Jan-Feb;25(1):62-7.	X3
13	Aminzadeh F. Adherence to recommendations of community-based comprehensive geriatric assessment programmes. Age Ageing. 2000 Sep;29(5):401-7.	X12
14	Anastasio GD, Little JM, Jr., Robinson MD, Pettice YL, Leitch BB, Norton HJ. Impact of compliance and side effects on the clinical outcome of patients treated with oral erythromycin. Pharmacotherapy. 1994 Mar-Apr;14(2):229-34.	X1
15	Andersen BL, Farrar WB, Golden-Kreutz DM, Glaser R, Emery CF, Crespin TR, et al. Psychological, behavioral, and immune changes after a psychological intervention: a clinical trial. J Clin Oncol. 2004 Sep 1;22(17):3570-80.	X13
16	Andersen BL, Yang HC, Farrar WB, Golden-Kreutz DM, Emery CF, Thornton LM, et al. Psychologic intervention improves survival for breast cancer patients: a randomized clinical trial. Cancer. 2008 Dec 15;113(12):3450-8.	X1
17	Andrejak M, Genes N, Vaur L, Poncelet P, Clerson P, Carre A. Electronic pill-boxes in the evaluation of antihypertensive treatment compliance: comparison of once daily versus twice daily regimen. Am J Hypertens. 2000 Feb;13(2):184-90.	X3
18	Anton RF, Moak DH, Waid LR, Latham PK, Malcolm RJ, Dias JK. Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics: results of a placebo-controlled trial. A J Psychiatry. 1999 Nov;156(11):1758-64.	X4
19	Antonicelli R, Mazzanti I, Abbatecola AM, Parati G. Impact of home patient telemonitoring on use of beta-blockers in congestive heart failure. Drugs Aging. 2010 Oct 1;27(10):801-5.	X12
20	Atherton-Naji A, Hamilton R, Riddle W, Naji S. Improving adherence to antidepressant drug treatment in primary care: a feasibility study for a randomized controlled trial of educational intervention. Primary Care Psychia. 2001 Jun;7(2):61-7.	X3
21	Aubert RE, Fulop G, Xia F, Thiel M, Maldonato D, Woo C. Evaluation of a depression health management program to improve outcomes in first or recurrent episode depression. Am J Manag Care. 2003 May;9(5):374-80.	X5
22	Audet MC, Moreau M, Koltun WD, Waldbaum AS, Shangold G, Fisher AC, et al. Evaluation of contraceptive efficacy and cycle control of a transdermal contraceptive patch vs an oral contraceptive: a randomized controlled trial. JAMA. 2001 May 9;285(18):2347-54.	X1
23	Babarykin D, Adamsone I, Amerika D, Spudass A, Moisejev V, Berzina N, et al. Calcium-enriched bread for treatment of uremic hyperphosphatemia. J Ren Nutr. 2004 Jul;14(3):149-56.	X1
24	Bailey B, Carney SL, Gillies AA, Smith AJ. Antihypertensive drug treatment: a comparison of usual care with self blood pressure measurement. J Hum Hypertens. 1999 Feb;13(2):147-50.	X3
25	Ball JR, Mitchell PB, Corry JC, Skillecorn A, Smith M, Malhi GS. A randomized controlled trial of cognitive therapy for bipolar disorder: focus on long-term change. J Clin Psychiatry. 2006 Feb;67(2):277-86.	X4
26	Bambauer KZ, Adams AS, Zhang F, Minkoff N, Grande A, Weisblatt R, et al. Physician alerts to increase antidepressant adherence: fax or fiction? Arch Intern Med. 2006 Mar 13;166(5):498-504.	X5
27	Bara-Carril N, Williams CJ, Pombo-Carril MG, Reid Y, Murray K, Aubin S, et al. A preliminary investigation into the feasibility and efficacy of a CD-ROM-based cognitive-behavioral self-help intervention for bulimia nervosa. Int J Eat Disord. 2004 May;35(4):538-48.	X1
28	Barnett CW, Nykamp D, Ellington AM. Patient-guided counseling in the community pharmacy setting. J Am Pharm Assoc (Wash). 2000 Nov-Dec;40(6):765-72.	X13
29	Barnett PG, Sorensen JL, Wong W, Haug NA, Hall SM. Effect of incentives for medication adherence on health care use and costs in methadone patients with HIV. Drug Alcohol Depend. 2009 Feb 1;100(1-2):115-21.	X4
30	Barrett B, Brown R, Rakel D, Mundt M, Bone K, Barlow S, et al. Echinacea for treating the common cold: a randomized trial. Ann Intern Med. 2010 Dec 21;153(12):769-77.	X1
31	Barron TI, Bennett K, Feely J. A competing risks prescription refill model of compliance and persistence. Value Health. 2010 Sep-Oct;13(6):796-804.	X2
32	Barrowclough C, Haddock G, Wykes T, Beardmore R, Conrod P, Craig T, et al. Integrated motivational interviewing and cognitive behavioural therapy for people with psychosis and comorbid substance misuse: randomised controlled trial. BMJ. 2010;341:c6325.	X1

	Study Information	Exclusion Code
33	Beaucage K, Lachance-Demers H, Ngo TT, Vachon C, Lamarre D, Guevin JF, et al. Telephone follow-up of patients receiving antibiotic prescriptions from community pharmacies. Am J Health Syst Pharm. 2006 Mar 15;63(6):557-63.	X3
34	Begley S, Livingstone C, Hodges N. Impact of domiciliary pharmacy visits on medication management in an elderly population. Int J Pharm Pract. 1997:111-21.	X3
35	Bennett H, Laird K, Margolius D, Ngo V, Thom DH, Bodenheimer T. The effectiveness of health coaching, home blood pressure monitoring, and home-titration in controlling hypertension among low-income patients: protocol for a randomized controlled trial. BMC public health. 2009;9:456.	X12
36	Bentz L, Enel P, Dunais B, Durant J, Poizot-Martin I, Tourette-Turgis C, et al. Evaluating counseling outcome on adherence to prophylaxis and follow-up after sexual HIV-risk exposure: a randomized controlled trial. AIDS Care. 2010 Dec;22(12):1509-16.	X3
37	Berg J, Dunbar-Jacob J, Rohay JM. Compliance with inhaled medications: the relationship between diary and electronic monitor. nn Behav Med. 1998 Winter;20(1):36-8.	X1
38	Berg KM, Mouriz J, Li X, Duggan E, Goldberg U, Arnsten JH. Rationale, design, and sample characteristics of a randomized controlled trial of directly observed antiretroviral therapy delivered in methadone clinics. Contemporary clinical trials. 2009 Sep;30(5):481-9.	X12
39	Berger S, Schad T, von Wyl V, Ehlert U, Zellweger C, Furrer H, et al. Effects of cognitive behavioral stress management on HIV-1 RNA, CD4 cell counts and psychosocial parameters of HIV-infected persons. AIDS. 2008 Mar 30;22(6):767-75.	X3
40	Berkowitz K, Peters R, Kjos SL, Goico J, Marroquin A, Dunn ME, et al. Effect of troglitazone on insulin sensitivity and pancreatic beta-cell function in women at high risk for NIDDM. Diabetes. 1996 Nov;45(11):1572-9.	X1
41	Berrien VM, Salazar JC, Reynolds E, McKay K. Adherence to antiretroviral therapy in HIV-infected pediatric patients improves with home-based intensive nursing intervention. Aids Patient Care STDS. 2004 Jun;18(6):355-63.	X13
42	Beswick AD, Rees K, West RR, Taylor FC, Burke M, Griebsch I, et al. Improving uptake and adherence in cardiac rehabilitation: literature review (Structured abstract). J Adv Nurs. 2005(5):538-55.	X1
43	Billault B, Degoulet P, Devries C, Plouin PF, Chatellier G, Menard J. Use of a standardized personal medical record by patients with hypertension: a randomized controlled prospective trial. MD Comput. 1995 Jan-Feb;12(1):31-5.	X3
44	Bocchi EA, Cruz F, Guimaraes G, Pinho Moreira LF, Issa VS, Ayub Ferreira SM, et al. Long-term prospective, randomized, controlled study using repetitive education at six-month intervals and monitoring for adherence in heart failure outpatients: the REMADHE trial. Circulation Heart failure. 2008 Jul;1(2):115-24.	X3
45	Boissel JP, Meillard O, Perrin-Fayolle E, Ducruet T, Alamercery Y, Sassano P, et al. Comparison between a bid and a tid regimen: improved compliance with no improved antihypertensive effect. The EOL Research Group. Eur J Clin Pharmacol. 1996;50(1-2):63-7.	X3
46	Borah B, Sacco P, Zarotsky V. Predictors of adherence among Alzheimer's disease patients receiving oral therapy. Curr Med Res Opin. 2010 Aug;26(8):1957-65.	X4
47	Bosch-Capblanch X, Abba K, Prictor M, Garner P. Contracts between patients and healthcare practitioners for improving patients' adherence to treatment, prevention and health promotion activities. Cochrane Database of Systematic Reviews. 2007(2).	X14
48	Bosworth HB, Olsen MK, Grubber JM, Neary AM, Orr MM, Powers BJ, et al. Two self-management interventions to improve hypertension control: a randomized trial. Ann Intern Med. 2009 Nov 17;151(10):687-95.	X12
49	Boudreau DM, Capoccia KL, Sullivan SD, Blough DK, Ellsworth AJ, Clark DL, et al. Collaborative care model to improve outcomes in major depression. Ann Pharmacother. 2002 Apr;36(4):585-91.	X9
50	Bradley-Ewing A, Thomson D, Pinkston M, Goggin KJ. A qualitative examination of the indirect effects of modified directly observed therapy on health behaviors other than adherence. Aids Patient Care STDS. 2008 Aug;22(8):663-8.	X5
51	Braun E, Baidusi A, Alroy G, Azzam ZS. Telephone follow-up improves patients satisfaction following hospital discharge. Eur J Intern Med. 2009 Mar;20(2):221-5.	X3
52	Braverman J, Dedier J. Predictors of medication adherence for African American patients diagnosed with hypertension. Ethn Dis. 2009 Autumn;19(4):396-400.	X5

	Study Information	Exclusion Code
53	Bright JI, Baker KD, Neimeyer RA. Professional and paraprofessional group treatments for depression: a comparison of cognitive-behavioral and mutual support interventions. J Consult Clin Psychol. 1999 Aug;67(4):491-501.	X1
54	Brown I, Sheeran P, Reuber M. Enhancing antiepileptic drug adherence: a randomized controlled trial. Epilepsy & behavior : E&B. 2009 Dec;16(4):634-9.	X3
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75	Chan V, Cooke CE. Pharmacotherapy after myocardial infarction: disease management versus usual care. Am J Manag Care. 2008 Jun;14(6):352-8.	X5
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82	Chiou PY, Kuo BI, Lee MB, Chen YM, Chuang P, Lin LC. A programme of symptom management for improving quality of life and drug adherence in AIDS/HIV patients. J Adv Nurs. 2006 Jul;55(2):169-79.	X3
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98	Cosman F, Borges JL, Curiel MD. Clinical evaluation of novel bisphosphonate dosing regimens in osteoporosis: the role of comparative studies and implications for future studies. Clin Ther. 2007 Jun;29(6):1116-27.	X5
99	Cote J, Bowie DM, Robichaud P, Parent JG, Battisti L, Boulet LP. Evaluation of two different educational interventions for adult patients consulting with an acute asthma exacerbation. Am J Respir Crit Care Med. 2001 May;163(6):1415-9.	X3
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102	Cramer J, Rosenheck R, Kirk G, Krol W, Krystal J. Medication compliance feedback and monitoring in a clinical trial: predictors and outcomes. Value Health. 2003 Sep-Oct;6(5):566-73.	X1
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104	Criswell TJ, Weber CA, Xu Y, Carter BL. Effect of self-efficacy and social support on adherence to antihypertensive drugs. Pharmacotherapy. 2010 May;30(5):432-41.	X5
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108	Datto CJ, Thompson R, Horowitz D, Disbot M, Oslin DW. The pilot study of a telephone disease management program for depression. Gen Hosp Psychiatry. 2003 May-Jun;25(3):169-77.	X7
109	Davis CE, Applegate WB, Gordon DJ, Curtis RC, McCormick M. An empirical evaluation of the placebo run-in. Control Clin Trials. 1995 Feb;16(1):41-50.	X1
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117	Delaronde S, Peruccio DL, Bauer BJ. Improving asthma treatment in a managed care population. Am J Manag Care. 2005 Jun;11(6):361-8.	X1
118	Delate T, Henderson R. Effect of patient notification of formulary change on formulary adherence. Journal of managed care pharmacy : JMCP. 2005 Jul-Aug;11(6):493-8.	X1
119	Delmas PD, Vrijens B, Eastell R, Roux C, Pols HA, Ringe JD, et al. Effect of monitoring bone turnover markers on persistence with risedronate treatment of postmenopausal osteoporosis. J Clin Endocrinol Metab. 2007 Apr;92(4):1296-304.	X3
120	Delp C, Jones J. Communicating information to patients: the use of cartoon illustrations to improve comprehension of instructions. Acad Emerg Med. 1996 Mar;3(3):264-70.	X4
121	Demyttenaere K, Mesters P, Boulanger B, Dewe W, Delsemme MH, Gregoire J, et al. Adherence to treatment regimen in depressed patients treated with amitriptyline or fluoxetine. J Affect Disord. 2001 Aug;65(3):243-52.	X1
122	Desplenter FA, Simoens S, Laekeman G. The impact of informing psychiatric patients about their medication: a systematic review (Structured abstract). Pharm World Sci. 2006(6):329-41.	X4
123	Devine EC. Meta-analysis of the effects of psychoeducational care in adults with asthma (Structured abstract). Res Nurs Health. 1996(5):367-76.	X4
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126	Dew MA, Goycoolea JM, Harris RC, Lee A, Zomak R, Dunbar-Jacob J, et al. An internet-based intervention to improve psychosocial outcomes in heart transplant recipients and family caregivers: development and evaluation. J Heart Lung Transplant. 2004 Jun;23(6):745-58.	X5
127	Dhillon V, Creiger J, Hannan J, Hurst N, Nuki G. The effect of DXA scanning on clinical decision making by general practitioners: a randomized, prospective trial of direct access versus referral to a hospital consultant. Osteoporos Int. 2003 Jun;14(4):326-33.	X3
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131	Doshi JA, Zhu J, Lee BY, Kimmel SE, Volpp KG. Impact of a prescription copayment increase on lipid-lowering medication adherence in veterans. Circulation. 2009 Jan 27;119(3):390-7.	X1
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133	du Treil S, Rice J, Leissinger CA. Quantifying adherence to treatment and its relationship to quality of life in a well-characterized haemophilia population. Haemophilia. 2007 Sep;13(5):493-501.	X1
134	Dunbar-Jacob J, Erlen JA, Schlenk EA, Ryan CM, Sereika SM, Doswell WM. Adherence in chronic disease. Annu Rev Nurs Res. 2000;18:48-90.	X5
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136	Dusing R, Handrock R, Klebs S, Tousset E, Vrijens B. Impact of supportive measures on drug adherence in patients with essential hypertension treated with valsartan: the randomized, open-label, parallel group study VALIDATE. J Hypertens. 2009 Apr;27(4):894-901.	X1
137	Ebbing M, Bonaa KH, Arnesen E, Ueland PM, Nordrehaug JE, Rasmussen K, et al. Combined analyses and extended follow-up of two randomized controlled homocysteine-lowering B-vitamin trials. J Intern Med. 2010 Oct;268(4):367-82.	X1
138	Edworthy SM, Baptie B, Galvin D, Brant RF, Churchill-Smith T, Manyari D, et al. Effects of an enhanced secondary prevention program for patients with heart disease: a prospective randomized trial. Can J Cardiol. 2007 Nov;23(13):1066-72.	X3
139	Edworthy SM, Devins GM. Improving medication adherence through patient education distinguishing between appropriate and inappropriate utilization. Patient Education Study Group. J Rheumatol. 1999 Aug;26(8):1793-801.	X3
140	Egan DA, Garg R, Wilt TJ, Pettinger MB, Davis KB, Crouse J, et al. Rationale and design of the Arterial Disease Multiple Intervention Trial (ADMIT) pilot study. Am J Cardiol. 1999 Feb 15;83(4):569-75.	X5
141	Elkjaer M, Shuhaibar M, Burisch J, Bailey Y, Scherfig H, Laugesen B, et al. E-health empowers patients with ulcerative colitis: a randomised controlled trial of the web-guided 'Constant-care' approach. Gut. 2010 Dec;59(12):1652-61.	X3
142	Ell K, Vourlekis B, Xie B, Nedjat-Haiem FR, Lee PJ, Muderspach L, et al. Cancer treatment adherence among low-income women with breast or gynecologic cancer: a randomized controlled trial of patient navigation. Cancer. 2009 Oct 1;115(19):4606-15.	X6
143	Eron JJ, Yetzer ES, Ruane PJ, Becker S, Sawyer GA, Fisher RL, et al. Efficacy, safety, and adherence with a twice-daily combination lamivudine/zidovudine tablet formulation, plus a protease inhibitor, in HIV infection. AIDS. 2000 Apr 14;14(6):671-81.	X1
144	Eussen SR, van der Elst ME, Klungel OH, Rompelberg CJ, Garssen J, Oosterveld MH, et al. A pharmaceutical care program to improve adherence to statin therapy: a randomized controlled trial. Ann Pharmacother. 2010 Dec;44(12):1905-13.	X3
145	Fabacher D, Josephson K, Pietruszka F, Linderborn K, Morley JE, Rubenstein LZ. An in-home preventive assessment program for independent older adults: a randomized controlled trial. J Am Geriatr Soc. 1994 Jun;42(6):630-8.	X12
146	Fairley CK, Levy R, Rayner CR, Allardice K, Costello K, Thomas C, et al. Randomized trial of an adherence programme for clients with HIV. Int J STD AIDS. 2003 Dec;14(12):805-9.	X4
147	Fallab-Stubi CL, Zellweger JP, Sauty A, Uldry C, Iorillo D, Burnier M. Electronic monitoring of adherence to treatment in the preventive chemotherapy of tuberculosis. Int J Tuberc Lung Dis. 1998 Jul;2(7):525-30.	X5
148	Farber H, Oliveria L. Trial of an asthma education program in an inner-city pediatric emergency department. Pediatr Asthma Allergy Immunol. 2004;17(2):107-15.	X13
149	Farmer AJ, Wade AN, French DP, Simon J, Yudkin P, Gray A, et al. Blood glucose self-monitoring in type 2 diabetes: a randomised controlled trial. Health Technol Assess. 2009 Feb;13(15):iii-iv, ix-xi, 1-50.	X3
150	Farup PG, Hovde O, Halvorsen FA, Raknerud N, Brodin U. Mesalazine suppositories versus hydrocortisone foam in patients with distal ulcerative colitis. A comparison of the efficacy and practicality of two topical treatment regimens. Scand J Gastroenterol. 1995 Feb;30(2):164-70.	X3
151	Faulkner MA, Wadibia EC, Lucas BD, Hilleman DE. Impact of pharmacy counseling on compliance and effectiveness of combination lipid-lowering therapy in patients undergoing coronary artery revascularization: a randomized, controlled trial. Pharmacotherapy. 2000 Apr;20(4):410-6.	X8
152	Feaster DJ, Brincks AM, Mitrani VB, Prado G, Schwartz SJ, Szapocznik J. The efficacy of structural ecosystems therapy for HIV medication adherence with African American women. Journal of family psychology : JFP : journal of the Division of Family Psychology of the American Psychological Association (Division 43). 2010 Feb;24(1):51-9.	X4
153	Fife KH, Barbarash RA, Rudolph T, Degregorio B, Roth R. Valaciclovir versus acyclovir in the treatment of first-episode genital herpes infection. Results of an international, multicenter, double-blind, randomized clinical trial. The Valaciclovir International Herpes Simplex Virus Study Group. Sex Transm Dis. 1997 Sep;24(8):481-6.	X4
154	Fihn SD, Bucher JB, McDonell M, Diehr P, Rumsfeld JS, Doak M, et al. Collaborative care intervention for stable ischemic heart disease. Arch Intern Med. 2011 Sep 12;171(16):1471-9.	X1

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155	Finkelstein JS, Wyland JJ, Lee H, Neer RM. Effects of teriparatide, alendronate, or both in women with postmenopausal osteoporosis. J Clin Endocrinol Metab. 2010 Apr;95(4):1838-45.	X1
156	Finley PR, Rens HR, Pont JT, Gess SL, Louie C, Bull SA, et al. Impact of a collaborative pharmacy practice model on the treatment of depression in primary care. Am J Health Syst Pharm. 2002 Aug 15;59(16):1518-26.	X5
157	Flandre P, Peytavin G, Meiffredy V, Saidi Y, Descamps D, Delagnes M, et al. Adherence to antiretroviral therapy and outcomes in HIV-infected patients enrolled in an induction/maintenance randomized trial. Antivir Ther. 2002 Jun;7(2):113-21.	X4
158	Fogarty L, Roter D, Larson S, Burke J, Gillespie J, Levy R. Patient adherence to HIV medication regimens: a review of published and abstract reports. Patient Educ Couns. 2002 Feb;46(2):93-108.	X5
159	Fogel NR, Weissberg-Benchell J. Preventing poor psychological and health outcomes in pediatric type 1 diabetes. Curr Diab Rep. 2010 Dec;10(6):436-43.	X13
160	Fonarow GC, Albert NM, Curtis AB, Stough WG, Gheorghiade M, Heywood JT, et al. Improving evidence-based care for heart failure in outpatient cardiology practices: primary results of the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF). Circulation. 2010 Aug 10;122(6):585-96.	X1
161	Fox PJ, Breuer W, Wright JA. Effects of a health promotion program on sustaining health behaviors in older adults. Am J Prev Med. 1997 Jul-Aug;13(4):257-64.	X1
162	Freeman EW, Rickels K, Sondheimer SJ, Polansky M, Xiao S. Continuous or intermittent dosing with sertraline for patients with severe premenstrual syndrome or premenstrual dysphoric disorder. A J Psychiatry. 2004 Feb;161(2):343-51.	X12
163	Fujioka K, Pans M, Joyal S. Glycemic control in patients with type 2 diabetes mellitus switched from twice-daily immediate-release metformin to a once-daily extended-release formulation. Clin Ther. 2003 Feb;25(2):515-29.	X1
164	Fumaz CR, Tuldra A, Ferrer MJ, Paredes R, Bonjoch A, Jou T, et al. Quality of life, emotional status, and adherence of HIV-1-infected patients treated with efavirenz versus protease inhibitor-containing regimens. J Acquir Immune Defic Syndr. 2002 Mar 1;29(3):244-53.	X4
165	Fungladda W, Honrado ER, Thimasarn K, Kitayaporn D, Karbwang J, Kamolratanakul P, et al. Compliance with artesunate and quinine + tetracycline treatment of uncomplicated falciparum malaria in Thailand. Bull World Health Organ. 1998;76 Suppl 1:59-66.	X3
166	Galan P, Kesse-Guyot E, Czernichow S, Briancon S, Blacher J, Hercberg S. Effects of B vitamins and omega 3 fatty acids on cardiovascular diseases: a randomised placebo controlled trial. BMJ. 2010;341:c6273.	X1
167	Gallefoss F, Bakke PS. How does patient education and self-management among asthmatics and patients with chronic obstructive pulmonary disease affect medication? Am J Respir Crit Care Med. 1999 Dec;160(6):2000-5.	X3
168	Gallefoss F, Bakke PS, Rsgaard PK. Quality of life assessment after patient education in a randomized controlled study on asthma and chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1999 Mar;159(3):812-7.	X1
169	Gallegos EC, Ovalle-Berumen F, Gomez-Meza MV. Metabolic control of adults with type 2 diabetes mellitus through education and counseling. J Nurs Scholarsh. 2006;38(4):344-51.	X5
170	Galliher JM, Post DM, Weiss BD, Dickinson LM, Manning BK, Staton EW, et al. Patients' question-asking behavior during primary care visits: a report from the AAFP National Research Network. Annals of family medicine. 2010 Mar-Apr;8(2):151-9.	X13
171	Garcia-Caballos M, Ramos-Diaz F, Jimenez-Moleon JJ, Bueno-Cavanillas A. Drug-related problems in older people after hospital discharge and interventions to reduce them. Age Ageing. 2010 Jul;39(4):430-8.	X14
172	Garland WH, Wohl AR, Valencia R, Witt MD, Squires K, Kovacs A, et al. The acceptability of a directly-administered antiretroviral therapy (DAART) intervention among patients in public HIV clinics in Los Angeles, California. AIDS Care. 2007 Feb;19(2):159-67.	X12
173	Gazmararian J, Jacobson KL, Pan Y, Schmotzer B, Kripalani S. Effect of a pharmacy-based health literacy intervention and patient characteristics on medication refill adherence in an urban health system. Ann Pharmacother. 2010 Jan;44(1):80-7.	X5
174	Gensichen J, Petersen JJ, Karroum T, Rauck S, Ludman E, Konig J, et al. Positive impact of a family practice-based depression case management on patient's self-management. Gen Hosp Psychiatry. 2011;33(1):23-8.	X3

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175	Gensichen J, von Korff M, Peitz M, Muth C, Beyer M, Guthlin C, et al. Case management for depression by health care assistants in small primary care practices: a cluster randomized trial. Ann Intern Med. 2009 Sep 15;151(6):369-78.	X3
176	George J, Elliott RA, Stewart DC. A systematic review of interventions to improve medication taking in elderly patients prescribed multiple medications. Drugs Aging. 2008;25(4):307-24.	X14
177	Gibson TB, Mark TL, Axelsen K, Baser O, Rublee DA, McGuigan KA. Impact of statin copayments on adherence and medical care utilization and expenditures. Am J Manag Care. 2006 Dec;12 Spec no.:SP11-9.	X2
178	Gibson TB, Song X, Alemayehu B, Wang SS, Waddell JL, Bouchard JR, et al. Cost sharing, adherence, and health outcomes in patients with diabetes. Am J Manag Care. 2010 Aug;16(8):589-600.	X5
179	Gilliam M, Knight S, McCarthy M, Jr. Success with oral contraceptives: a pilot study. Contraception. 2004 May;69(5):413-8.	X13
180	Gilutz H, Novack L, Shvartzman P, Zelingher J, Bonneh DY, Henkin Y, et al. Computerized community cholesterol control (4C): meeting the challenge of secondary prevention. Isr Med Assoc J. 2009 Jan;11(1):23-9.	X1
181	Girvin BG, Johnston GD. Comparison of the effects of a 7-day period of non-compliance on blood pressure control using three different antihypertensive agents. J Hypertens. 2004 Jul;22(7):1409-14.	X3
182	Glaser NS, Iden SB, Green-Burgeson D, Bennett C, Hood-Johnson K, Styne DM, et al. Benefits of an insulin dosage calculation device for adolescents with type 1 diabetes mellitus. J Pediatr Endocrinol Metab. 2004 Dec;17(12):1641-51.	X13
183	Glasgow RE, Boles SM, McKay HG, Feil EG, Barrera M, Jr. The D-Net diabetes self-management program: long-term implementation, outcomes, and generalization results. Prev Med. 2003 Apr;36(4):410-9.	X1
184	Glasgow RE, Christiansen SM, Kurz D, King DK, Woolley T, Faber AJ, et al. Engagement in a diabetes self-management website: usage patterns and generalizability of program use. Journal of medical Internet research. 2011;13(1):e9.	X5
185	Godleski LS, Goldsmith LJ, Vieweg WV, Zettwoch NC, Stikovac DM, Lewis SJ. Switching from depot antipsychotic drugs to olanzapine in patients with chronic schizophrenia. J Clin Psychiatry. 2003 Feb;64(2):119-22.	X1
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187	Goldbach-Mansky R, Wilson M, Fleischmann R, Olsen N, Silverfield J, Kempf P, et al. Comparison of Tripterygium wilfordii Hook F versus sulfasalazine in the treatment of rheumatoid arthritis: a randomized trial. Ann Intern Med. 2009 Aug 18;151(4):229-40, W49-51.	X1
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190	Golin CE, Earp J, Tien HC, Stewart P, Porter C, Howie L. A 2-arm, randomized, controlled trial of a motivational interviewing-based intervention to improve adherence to antiretroviral therapy (ART) among patients failing or initiating ART. J Acquir Immune Defic Syndr. 2006 May;42(1):42-51.	X4
191	Goodyer LI, Miskelly F, Milligan P. Does encouraging good compliance improve patients' clinical condition in heart failure? Br J Clin Pract. 1995 Jul-Aug;49(4):173-6.	X3
192	Goujard C, Bernard N, Sohier N, Peyramond D, Lancon F, Chwalow J, et al. Impact of a patient education program on adherence to HIV medication: a randomized clinical trial. J Acquir Immune Defic Syndr. 2003 Oct 1;34(2):191-4.	X3
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194	Gray Trish A, Orton Lois C, Henson D, Harper R, Waterman H. Interventions for improving adherence to ocular hypotensive therapy. Cochrane Database of Systematic Reviews. 2009(2).	X14

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195	Graziano JA, Gross CR. The effects of isolated telephone interventions on glycemic control in type 2 diabetes: a literature review. ANS Adv Nurs Sci. 2009 Jul-Sep;32(3):E28-41.	X12
196	Gross R, Tierney C, Andrade A, Lalama C, Rosenkranz S, Eshleman SH, et al. Modified directly observed antiretroviral therapy compared with self-administered therapy in treatment-naive HIV-1-infected patients: a randomized trial. Arch Intern Med. 2009 Jul 13;169(13):1224-32.	X4
197	Grosset KA, Bone I, Reid JL, Grosset D. Measuring therapy adherence in Parkinson's disease: a comparison of methods. J Neurol Neurosurg Psychiatry. 2006 Feb;77(2):249-51.	X3
198	Grosset KA, Grosset DG. Effect of educational intervention on medication timing in Parkinson's disease: a randomized controlled trial. BMC neurology. 2007;7:20.	X3
199	Guerci B, Drouin P, Grange V, Bougneres P, Fontaine P, Kerlan V, et al. Self-monitoring of blood glucose significantly improves metabolic control in patients with type 2 diabetes mellitus: the Auto-Surveillance Intervention Active (ASIA) study. Diabetes Metab. 2003 Dec;29(6):587-94.	X1
200	Guilera M, Fuentes M, Grifols M, Ferrer J, Badia X. Does an educational leaflet improve self-reported adherence to therapy in osteoporosis? The OPTIMA study. Osteoporos Int. 2006;17(5):664-71.	X3
201	Gump BB, Matthews KA. Special intervention reduces CVD mortality for adherent participants in the multiple risk factor intervention trial. nn Behav Med. 2003 Aug;26(1):61-8.	X1
202	Guo X, Zhai J, Liu Z, Fang M, Wang B, Wang C, et al. Effect of antipsychotic medication alone vs combined with psychosocial intervention on outcomes of early-stage schizophrenia: A randomized, 1-year study. Arch Gen Psychiatry. 2010 Sep;67(9):895-904.	X3
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205	Hamann J, Cohen R, Leucht S, Busch R, Kissling W. Shared decision making and long-term outcome in schizophrenia treatment. J Clin Psychiatry. 2007 Jul;68(7):992-7.	X3
206	Hanlon JT, Weinberger M, Samsa GP, Schmader KE, Uttech KM, Lewis IK, et al. A randomized, controlled trial of a clinical pharmacist intervention to improve inappropriate prescribing in elderly outpatients with polypharmacy. Am J Med. 1996 Apr;100(4):428-37.	X1
207	Hansen RA, Kim MM, Song L, Tu W, Wu J, Murray MD. Comparison of methods to assess medication adherence and classify nonadherence. Ann Pharmacother. 2009 Mar;43(3):413-22.	X1
208	Hardstaff R, Green K, Talbot D. Measurement of compliance posttransplantation--the results of a 12-month study using electronic monitoring. Transplant Proc. 2003 Mar;35(2):796-7.	X3
209	Harrington J, Noble LM, Newman SP. Improving patients' communication with doctors: a systematic review of intervention studies. Patient Educ Couns. 2004 Jan;52(1):7-16.	X12
210	Harris SB, Leiter LA, Webster-Bogaert S, Van DM, O'Neill C. Teleconferenced educational detailing: diabetes education for primary care physicians. J Contin Educ Health Prof. 2005 Spring;25(2):87-97.	X1
211	Hawkes AL, Atherton J, Taylor CB, Scuffham P, Eadie K, Miller NH, et al. Randomised controlled trial of a secondary prevention program for myocardial infarction patients ('ProActive Heart'): study protocol. Secondary prevention program for myocardial infarction patients. BMC Cardiovasc Disord. 2009;9:16.	X12
212	Hawthorne AB, Rubin G, Ghosh S. Review article: medication non-adherence in ulcerative colitis--strategies to improve adherence with mesalazine and other maintenance therapies. Aliment Pharmacol Ther. 2008 Jun;27(12):1157-66.	X9
213	Haynes RB, Ackloo E, Sahota N, McDonald Heather P, Yao X. Interventions for enhancing medication adherence. Cochrane Database of Systematic Reviews. 2008(2).	X14
214	Haynes RB, McKibbon KA, Kanani R. Systematic review of randomised trials of interventions to assist patients to follow prescriptions for medications (Brief record). Lancet. 1996(9024):383-6.	X10
215	He J, Streiffer RH, Muntner P, Krousel-Wood MA, Whelton PK. Effect of dietary fiber intake on blood pressure: a randomized, double-blind, placebo-controlled trial. J Hypertens. 2004 Jan;22(1):73-80.	X1

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216	Hedrick SC, Chaney EF, Felker B, Liu CF, Hasenberg N, Heagerty P, et al. Effectiveness of collaborative care depression treatment in Veterans' Affairs primary care. J Gen Intern Med. 2003 Jan;18(1):9-16.	X1
217	Heffner JL, Tran GQ, Johnson CS, Barrett SW, Blom TJ, Thompson RD, et al. Combining motivational interviewing with compliance enhancement therapy (MI-CET): development and preliminary evaluation of a new, manual-guided psychosocial adjunct to alcohol-dependence pharmacotherapy. J Stud Alcohol Drugs. 2010 Jan;71(1):61-70.	X1
218	Heneghan Carl J, Glasziou Paul P, Perera R. Reminder packaging for improving adherence to self-administered long-term medications. Cochrane Database of Systematic Reviews. 2006(1).	X14
219	Hill J, Bird H, Johnson S. Effect of patient education on adherence to drug treatment for rheumatoid arthritis: a randomised controlled trial. Ann Rheum Dis. 2001 Sep;60(9):869-75.	X3
220	Hirsch JD, Rosenquist A, Best BM, Miller TA, Gilmer TP. Evaluation of the first year of a pilot program in community pharmacy: HIV/AIDS medication therapy management for Medi-Cal beneficiaries. Journal of managed care pharmacy : JMCP. 2009 Jan-Feb;15(1):32-41.	X4
221	Holzemer WL, Bakken S, Portillo CJ, Grimes R, Welch J, Wantland D, et al. Testing a nurse-tailored HIV medication adherence intervention. Nurs Res. 2006 May-Jun;55(3):189-97.	X4
222	Homer D, Nightingale P, Jobanputra P. Providing patients with information about disease-modifying anti-rheumatic drugs: Individually or in groups? A pilot randomized controlled trial comparing adherence and satisfaction. Musculoskeletal Care. 2009 Jun;7(2):78-92.	X3
223	Hornnes N, Larsen K, Boysen G. Blood pressure 1 year after stroke: the need to optimize secondary prevention. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association. 2011 Jan-Feb;20(1):16-23.	X3
224	Hornung WP, Kieserg A, Feldmann R, Buchkremer G. Psychoeducational training for schizophrenic patients: background, procedure and empirical findings. Patient Educ Couns. 1996 Dec;29(3):257-68.	X4
225	Hornung WP, Klingberg S, Feldmann R, Schonauer K, Schulze Monking H. Collaboration with drug treatment by schizophrenic patients with and without psychoeducational training: results of a 1-year follow-up. Acta Psychiatr Scand. 1998 Mar;97(3):213-9.	X4
226	Hou MY, Hurwitz S, Kavanagh E, Fortin J, Goldberg AB. Using daily text-message reminders to improve adherence with oral contraceptives: a randomized controlled trial. Obstet Gynecol. 2010 Sep;116(3):633-40.	X13
227	Hudson TJ, Owen RR, Thrush CR, Armitage TL, Thapa P. Guideline implementation and patient-tailoring strategies to improve medication adherence for schizophrenia. J Clin Psychiatry. 2008 Jan;69(1):74-80.	X4
228	Hudson TJ, Owen RR, Thrush CR, Han X, Pyne JM, Thapa P, et al. A pilot study of barriers to medication adherence in schizophrenia. J Clin Psychiatry. 2004 Feb;65(2):211-6.	X2
229	Huffman JC, Mastromauro CA, Sowden G, Fricchione GL, Healy BC, Januzzi JL. Impact of a depression care management program for hospitalized cardiac patients. Circulation Cardiovascular quality and outcomes. 2011 Mar;4(2):198-205.	X1
230	Hulse GK, Ngo HT, Tait RJ. Risk factors for craving and relapse in heroin users treated with oral or implant naltrexone. Biol Psychiatry. 2010 Aug 1;68(3):296-302.	X12
231	Huskamp HA, Deverka PA, Landrum MB, Epstein RS, McGuigan KA. The effect of three-tier formulary adoption on medication continuation and spending among elderly retirees. Health Serv Res. 2007 Oct;42(5):1926-42.	X1
232	Hwang LY, Grimes CZ, Tran TQ, Clark A, Xia R, Lai D, et al. Accelerated hepatitis B vaccination schedule among drug users: a randomized controlled trial. J Infect Dis. 2010 Nov 15;202(10):1500-9.	X13
233	Imaz I, Zegarra P, Gonzalez-Enriquez J, Rubio B, Alcazar R, Amate JM. Poor bisphosphonate adherence for treatment of osteoporosis increases fracture risk: systematic review and meta-analysis (Provisional abstract). Osteoporos Int. 2010(11):1943-51.	X1
234	Ingersoll KS, Cropsey KL, Heckman CJ. A test of motivational plus nicotine replacement interventions for HIV positive smokers. AIDS and behavior. 2009 Jun;13(3):545-54.	X1
235	Ironson G, Weiss S, Lydston D, Ishii M, Jones D, Asthana D, et al. The impact of improved self-efficacy on HIV viral load and distress in culturally diverse women living with AIDS: the SMART/EST Women's Project. AIDS Care. 2005 Feb;17(2):222-36.	X12

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236	Iskedjian M, Einarson TR, MacKeigan LD, Shear N, Addis A, Mittmann N, et al. Relationship between daily dose frequency and adherence to antihypertensive pharmacotherapy: evidence from a meta analysis (Structured abstract). Clin Ther. 2002(2):302-16.	X14
237	Jackson C, Lawton RJ, Raynor DK, Knapp P, Conner MT, Lowe CJ, et al. Promoting adherence to antibiotics: a test of implementation intentions. Patient Educ Couns. 2006 May;61(2):212-8.	X4
238	Jameson J, VanNoord G, Vanderwoud K. The impact of a pharmacotherapy consultation on the cost and outcome of medical therapy. J Fam Pract. 1995 Nov;41(5):469-72.	X12
239	Jameson JP, Baty PJ. Pharmacist collaborative management of poorly controlled diabetes mellitus: a randomized controlled trial. Am J Manag Care. 2010 Apr;16(4):250-5.	X1
240	Jamison RN, Ross EL, Michna E, Chen LQ, Holcomb C, Wasan AD. Substance misuse treatment for high-risk chronic pain patients on opioid therapy: a randomized trial. Pain. 2010 Sep;150(3):390-400.	X1
241	Jansen A, Andersen KF, Bruning H. Evaluation of a compliance device in a subgroup of adult patients receiving specific immunotherapy with grass allergen tablets (GRAZAX) in a randomized, open-label, controlled study: an a priori subgroup analysis. Clin Ther. 2009 Feb;31(2):321-7.	X3
242	Janssen MJ, van der Kuy A, ter Wee PM, van Boven WP. Aluminum hydroxide, calcium carbonate and calcium acetate in chronic intermittent hemodialysis patients. Clin Nephrol. 1996 Feb;45(2):111-9.	X3
243	Javanbakht M, Prosser P, Grimes T, Weinstein M, Farthing C. Efficacy of an individualized adherence support program with contingent reinforcement among nonadherent HIV-positive patients: results from a randomized trial. J Int Assoc Physicians AIDS Care (Chic). 2006 Dec;5(4):143-50.	X12
244	Johns SA, Kroenke K, Theobald DE, Wu J, Tu W. Telecare management of pain and depression in patients with cancer: patient satisfaction and predictors of use. The Journal of ambulatory care management. 2011 Apr-Jun;34(2):126-39.	X1
245	Johnson BA, Ait-Daoud N, Aubin HJ, Van Den Brink W, Guzzetta R, Loewy J, et al. A pilot evaluation of the safety and tolerability of repeat dose administration of long-acting injectable naltrexone (Vivitrex) in patients with alcohol dependence. Alcohol Clin Exp Res. 2004 Sep;28(9):1356-61.	X8
246	Johnson CJ, Heckman TG, Hansen NB, Kochman A, Sikkema KJ. Adherence to antiretroviral medication in older adults living with HIV/AIDS: a comparison of alternative models. AIDS Care. 2009 May;21(5):541-51.	X1
247	Johnson KA, Chen S, Cheng IN, Lou M, Gregerson P, Blieden C, et al. The impact of clinical pharmacy services integrated into medical homes on diabetes-related clinical outcomes. Ann Pharmacother. 2010 Dec;44(12):1877-86.	X1
248	Johnson MO, Charlebois E, Morin SF, Remien RH, Chesney MA. Effects of a behavioral intervention on antiretroviral medication adherence among people living with HIV: the healthy living project randomized controlled study. J Acquir Immune Defic Syndr. 2007 Dec 15;46(5):574-80.	X4
249	Johnson MO, Gamarel KE, Dawson Rose C. Changing HIV treatment expectancies: a pilot study. AIDS Care. 2006 Aug;18(6):550-3.	X8
250	Jones DL, Ishii M, LaPerriere A, Stanley H, Antoni M, Ironson G, et al. Influencing medication adherence among women with AIDS. AIDS Care. 2003 Aug;15(4):463-74.	X4
251	Joos SK, Hickam DH, Gordon GH, Baker LH. Effects of a physician communication intervention on patient care outcomes. J Gen Intern Med. 1996 Mar;11(3):147-55.	X5
252	Joosten EA, DeFuentes-Merillas L, de W, G H, Sensky T, van der Staak CP, et al. Systematic review of the effects of shared decision-making on patient satisfaction, treatment adherence and health status (Structured abstract). Psychother Psychosom. 2008(4):219-26.	X1
253	Jorgensen P, Nordentoft M, Abel MB, Gouliaev G, Jeppesen P, Kassow P. Early detection and assertive community treatment of young psychotics: the Opus Study Rationale and design of the trial. Soc Psychiatry Psychiatr Epidemiol. 2000 Jul;35(7):283-7.	X12
254	Jovicic A, Holroyd-Leduc JM, Straus SE. Effects of self-management intervention on health outcomes of patients with heart failure: a systematic review of randomized controlled trials (Structured abstract). BMC Cardiovascular Disorders. 2006.	X1

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255	Kaboli P, Hoth A, Carter BL, Chrischilles EA, Shorr RI, Bhattacharyya A, et al. The VA Enhanced Pharmacy Outpatient Clinic (EPOC) Study: A randomized-controlled pharmacist-physician intervention trial. J Gen Intern Med. 2004 Apr;19(Suppl 1):227.	X9
256	Kalichman SC, Cherry C, Kalichman MO, Amaral CM, White D, Pope H, et al. Integrated behavioral intervention to improve HIV/AIDS treatment adherence and reduce HIV transmission. Am J Public Health. 2011 Mar;101(3):531-8.	X4
257	Kalsekar I, Iyer S, Mody R, Rajagopalan R, Kavookjian J. Utilization and costs for compliant patients initiating therapy with pioglitazone or rosiglitazone versus insulin in a Medicaid fee-for-service population. Journal of managed care pharmacy : JMCP. 2006 Mar;12(2):121-9.	X5
258	Kaplan B, Mason NA, Shimp LA, Ascione FJ. Chronic hemodialysis patients. Part I: Characterization and drug-related problems. Ann Pharmacother. 1994 Mar;28(3):316-9.	X8
259	Karkkainen MK, Tuppurainen M, Salovaara K, Sandini L, Rikkonen T, Sirola J, et al. Does daily vitamin D 800 IU and calcium 1000 mg supplementation decrease the risk of falling in ambulatory women aged 65-71 years? A 3-year randomized population-based trial (OSTPRE-FPS). Maturitas. 2010 Apr;65(4):359-65.	X1
260	Kastrissios H, Suarez JR, Hammer S, Katzenstein D, Blaschke TF. The extent of non-adherence in a large AIDS clinical trial using plasma dideoxynucleoside concentrations as a marker. AIDS. 1998 Dec 3;12(17):2305-11.	X4
261	Katlama C, Fenske S, Gazzard B, Lazzarin A, Clumeck N, Mallolas J, et al. TRIZAL study: switching from successful HAART to Trizivir (abacavir-lamivudine-zidovudine combination tablet): 48 weeks efficacy, safety and adherence results. HIV Med. 2003 Apr;4(2):79-86.	X4
262	Kato PM, Cole SW, Bradlyn AS, Pollock BH. A video game improves behavioral outcomes in adolescents and young adults with cancer: a randomized trial. Pediatrics. 2008 Aug;122(2):e305-17.	X3
263	Katzelnick DJ, Simon GE, Pearson SD, Manning WG, Helstad CP, Henk HJ, et al. Randomized trial of a depression management program in high utilizers of medical care. Arch Fam Med. 2000 Apr;9(4):345-51.	X1
264	Kemp R, David A. Psychological predictors of insight and compliance in psychotic patients. Br J Psychiatry. 1996 Oct;169(4):444-50.	X6
265	Kemp R, Kirov G, Everitt B, Hayward P, David A. Randomised controlled trial of compliance therapy. 18-month follow-up. Br J Psychiatry. 1998 May;172:413-9.	X3
266	Kendler D, Kung AW, Fuleihan Gel H, Gonzalez Gonzalez JG, Gaines KA, Verbruggen N, et al. Patients with osteoporosis prefer once weekly to once daily dosing with alendronate. Maturitas. 2004 Jul 15;48(3):243-51.	X3
267	Kennedy TM, Chalder T, McCrone P, Darnley S, Knapp M, Jones RH, et al. Cognitive behavioural therapy in addition to antispasmodic therapy for irritable bowel syndrome in primary care: randomised controlled trial. Health Technol Assess. 2006 Jun;10(19):iii-iv, ix-x, 1-67.	X1
268	Kenny AM, Kleppinger A, Annis K, Rathier M, Browner B, Judge JO, et al. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels, low bone mass, and physical frailty. J Am Geriatr Soc. 2010 Jun;58(6):1134-43.	X1
269	Kenny AM, Mangano KM, Abourizk RH, Bruno RS, Anamani DE, Kleppinger A, et al. Soy proteins and isoflavones affect bone mineral density in older women: a randomized controlled trial. Am J Clin Nutr. 2009 Jul;90(1):234-42.	X1
270	Kiarie JN, Kreiss JK, Richardson BA, John-Stewart GC. Compliance with antiretroviral regimens to prevent perinatal HIV-1 transmission in Kenya. AIDS. 2003 Jan 3;17(1):65-71.	X3
271	Kidder DP, Wolitski RJ, Royal S, Aidala A, Courtenay-Quirk C, Holtgrave DR, et al. Access to housing as a structural intervention for homeless and unstably housed people living with HIV: rationale, methods, and implementation of the housing and health study. AIDS and behavior. 2007 Nov;11(6 Suppl):149-61.	X12
272	Kim B, Lee SH, Choi TK, Suh S, Kim YW, Lee E, et al. Effectiveness of risperidone long-acting injection in first-episode schizophrenia: in naturalistic setting. Prog Neuropsychopharmacol Bol Psychiatry. 2008 Jul 1;32(5):1231-5.	X5
273	Kimmelstiel C, Levine D, Perry K, Patel AR, Sadaniantz A, Gorham N, et al. Randomized, controlled evaluation of short- and long-term benefits of heart failure disease management within a diverse provider network: the SPAN-CHF trial. Circulation. 2004 Sep 14;110(11):1450-5.	X12

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274	King AB, Wolfe GS. Evaluation of a diabetes specialist-guided primary care diabetes treatment program. J Am Acad Nurse Pract. 2009 Jan;21(1):24-30.	X12
275	Kirkman MS, Weinberger M, Landsman PB, Samsa GP, Shortliffe EA, Simel DL, et al. A telephone-delivered intervention for patients with NIDDM. Effect on coronary risk factors. Diabetes Care. 1994 Aug;17(8):840-6.	X12
276	Klein A, Otto G, Kramer I. Impact of a pharmaceutical care program on liver transplant patientsg(euro)(trademark) compliance with immunosuppressive medication: A prospective, randomized, controlled trial using electronic monitoring. Transplantation. 2009;87(6):839-47.	X3
277	Ko SH, Song KH, Kim SR, Lee JM, Kim JS, Shin JH, et al. Long-term effects of a structured intensive diabetes education programme (SIDEP) in patients with Type 2 diabetes mellitus--a 4-year follow-up study. Diabet Med. 2007 Jan;24(1):55-62.	X1
278	Koelling TM, Johnson ML, Cody RJ, Aaronson KD. Discharge education improves clinical outcomes in patients with chronic heart failure. Circulation. 2005 Jan 18;111(2):179-85.	X12
279	Koenig LJ, Pals SL, Bush T, Pratt Palmore M, Stratford D, Ellerbrock TV. Randomized controlled trial of an intervention to prevent adherence failure among HIV-infected patients initiating antiretroviral therapy. Health Psychol. 2008 Mar;27(2):159-69.	X4
280	Kothawala P, Badamgarav E, Ryu S, Miller RM, Halbert RJ. Systematic review and meta-analysis of real-world adherence to drug therapy for osteoporosis (Structured abstract). Mayo Clin Proc. 2007(12):1493-501.	X5
281	Kotowycz MA, Cosman TL, Tartaglia C, Afzal R, Syal RP, Natarajan MK. Safety and feasibility of early hospital discharge in ST-segment elevation myocardial infarction--a prospective and randomized trial in low-risk primary percutaneous coronary intervention patients (the Safe-Depart Trial). Am Heart J. 2010 Jan;159(1):117 e1-6.	X1
282	Kozuki Y, Schepp KG. Visual-feedback therapy for antipsychotic medication adherence. Int Clin Psychopharmacol. 2006 Jan;21(1):57-61.	X8
283	Krier BP, Parker RD, Grayson D, Byrd G. Effect of diabetes education on glucose control. J La State Med Soc. 1999 Feb;151(2):86-92.	X1
284	Kripalani S, Robertson R, Love-Ghaffari MH, Henderson LE, Praska J, Strawder A, et al. Development of an illustrated medication schedule as a low-literacy patient education tool. Patient Educ Couns. 2007 Jun;66(3):368-77.	X5
285	Kripalani S, Yao X, Haynes B. Interventions to enhance medication adherence in chronic medical conditions (Brief record). Arch Intern Med. 2007(6):540-50.	X14
286	Krueger KP, Felkey BG, Berger BA. Improving adherence and persistence: a review and assessment of interventions and description of steps toward a national adherence initiative. J Am Pharm Assoc (2003). 2003 Nov-Dec;43(6):668-78; quiz 78-9.	X9
287	Kruk ME, Schwalbe N. The relation between intermittent dosing and adherence: preliminary insights (Provisional abstract). Clin Ther. 2006(12):1989-95.	X14
288	Kuo S, Burrill J. Differences in antihypertensive compliance by BCBSRI disease and case management intervention group. Med Health R I. 2007 Dec;90(12):381-4.	X5
289	Kurtz S, Shemesh G. The efficacy and safety of once-daily versus once-weekly latanoprost treatment for increased intraocular pressure. J Ocul Pharmacol Ther. 2004 Aug;20(4):321-7.	X8
290	Kutzleb J, Reiner D. The impact of nurse-directed patient education on quality of life and functional capacity in people with heart failure. J Am Acad Nurse Pract. 2006 Mar;18(3):116-23.	X8
291	LaCroix AZ, Kotchen J, Anderson G, Brzyski R, Cauley JA, Cummings SR, et al. Calcium plus vitamin D supplementation and mortality in postmenopausal women: the Women's Health Initiative calcium-vitamin D randomized controlled trial. J Gerontol A Biol Sci Med Sci. 2009 May;64(5):559-67.	X1
292	Lai LL. Community pharmacy-based hypertension disease-management program in a Latino/Hispanic-American population. Consult Pharm. 2007 May;22(5):411-6.	X5
293	Lai P, Chua SS, Chan SP. A systematic review of interventions by healthcare professionals on community-dwelling postmenopausal women with osteoporosis (Provisional abstract). Osteoporos Int. 2010(10):1637-56.	X1
294	Laine L, Connors L, Griffin MR, Curtis SP, Kaur A, Cannon CP. Prescription rates of protective co-therapy for NSAID users at high GI risk and results of attempts to improve adherence to guidelines. Aliment Pharmacol Ther. 2009 Oct;30(7):767-74.	X1

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295	Lam DH, Watkins ER, Hayward P, Bright J, Wright K, Kerr N, et al. A randomized controlled study of cognitive therapy for relapse prevention for bipolar affective disorder: outcome of the first year. Arch Gen Psychiatry. 2003 Feb;60(2):145-52.	X4
296	Laporte S, Quenet S, Buchmuller-Cordier A, Reynaud J, Tardy-Poncet B, Thirion C, et al. Compliance and stability of INR of two oral anticoagulants with different half-lives: a randomised trial. Thromb Haemost. 2003 Mar;89(3):458-67.	X1
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301	Leenen FH, Wilson TW, Bolli P, Larochelle P, Myers M, Handa SP, et al. Patterns of compliance with once versus twice daily antihypertensive drug therapy in primary care: a randomized clinical trial using electronic monitoring. Can J Cardiol. 1997 Oct;13(10):914-20.	X3
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315	Liu Q, Abba K, Alejandria Marissa M, Balanag Vincent M, Berba Regina P, Lansang Mary Ann D. Reminder systems and late patient tracers in the diagnosis and management of tuberculosis. Cochrane Database of Systematic Reviews. 2008(4).	X4
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318	Lopez Cabezas C, Falces Salvador C, Cubi Quadrada D, Arnau Bartes A, Ylla Bore M, Muro Perea N, et al. Randomized clinical trial of a postdischarge pharmaceutical care program vs regular follow-up in patients with heart failure. Farm Hosp. 2006 Nov-Dec;30(6):328-42.	X3
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330	Mahtani Kamal R, Heneghan Carl J, Glasziou Paul P, Perera R. Reminder packaging for improving adherence to self-administered long-term medications. Cochrane Database of Systematic Reviews. 2011(9).	X10
331	Maier C, Mustapic D, Schuster E, Luger A, Eher R. Effect of a pocket-size tablet-dispensing device on glycaemic control in Type 2 diabetic patients. Diabet Med. 2006 Jan;23(1):40-5.	X12
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337	Mannheimer SB, Morse E, Matts JP, Andrews L, Child C, Schmetter B, et al. Sustained benefit from a long-term antiretroviral adherence intervention. Results of a large randomized clinical trial. J Acquir Immune Defic Syndr. 2006 Dec 1;43 Suppl 1:S41-7.	X4
338	Man-Son-Hing M, Laupacis A, O'Connor AM, Biggs J, Drake E, Yetisir E, et al. A patient decision aid regarding antithrombotic therapy for stroke prevention in atrial fibrillation: a randomized controlled trial. JAMA. 1999 Aug 25;282(8):737-43.	X1
339	Mansoor LE, Dowse R. Medicines information and adherence in HIV/AIDS patients. J Clin Pharm Ther. 2006 Feb;31(1):7-15.	X4
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342	Marlowe DB, Kirby KC, Festinger DS, Merikle EP, Tran GQ, Platt JJ. Day treatment for cocaine dependence: incremental utility over outpatient counseling and voucher incentives. Addict Behav. 2003 Mar;28(2):387-98.	X1
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344	Martino S, Carroll KM, Nich C, Rounsaville BJ. A randomized controlled pilot study of motivational interviewing for patients with psychotic and drug use disorders. Addiction. 2006 Oct;101(10):1479-92.	X4
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346	Matteson ML, Russell C. Interventions to improve hemodialysis adherence: a systematic review of randomized-controlled trials (Provisional abstract). Hemodialysis International. 2010(4):370-82.	X1
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349	McDonald HP, Garg AX, Haynes RB. Interventions to enhance patient adherence to medication prescriptions (Brief record). JAMA. 2002(22):2868-78.	X14
350	McDonough RP, Doucette WR. Drug therapy management: an empirical report of drug therapy problems, pharmacists' interventions, and results of pharmacists' actions. J Am Pharm Assoc (2003). 2003 Jul-Aug;43(4):511-8.	X7
351	McIntosh A, Conlon L, Lawrie S, Stanfield Andrew C. Compliance therapy for schizophrenia. Cochrane Database of Systematic Reviews. 2006(3).	X4
352	McMurdo ME, Price RJ, Shields M, Potter J, Stott DJ. Should oral nutritional supplementation be given to undernourished older people upon hospital discharge? A controlled trial. J Am Geriatr Soc. 2009 Dec;57(12):2239-45.	X1
353	Mehos BM, Saseen JJ, MacLaughlin EJ. Effect of pharmacist intervention and initiation of home blood pressure monitoring in patients with uncontrolled hypertension. Pharmacotherapy. 2000 Nov;20(11):1384-9.	X8
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356	Miklowitz DJ, George EL, Richards JA, Simoneau TL, Suddath RL. A randomized study of family-focused psychoeducation and pharmacotherapy in the outpatient management of bipolar disorder. Arch Gen Psychiatry. 2003 Sep;60(9):904-12.	X4

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358	Mitrani VB, McCabe BE, Robinson C, Weiss-Laxer NS, Feaster DJ. Structural Ecosystems Therapy for recovering HIV-positive women: child, mother, and parenting outcomes. Journal of family psychology : JFP : journal of the Division of Family Psychology of the American Psychological Association (Division 43). 2010 Dec;24(6):746-55.	X12
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360	Mohamed S, Rosenheck R, McEvoy J, Swartz M, Stroup S, Lieberman JA. Cross-sectional and longitudinal relationships between insight and attitudes toward medication and clinical outcomes in chronic schizophrenia. Schizophr Bull. 2009 Mar;35(2):336-46.	X1
361	Montgomery EB, Jr., Lieberman A, Singh G, Fries JF. Patient education and health promotion can be effective in Parkinson's disease: a randomized controlled trial. PROPATH Advisory Board. Am J Med. 1994 Nov;97(5):429-35.	X12
362	Mooney ME, Sayre SL, Hokanson PS, Stotts AL, Schmitz JM. Adding MEMS feedback to behavioral smoking cessation therapy increases compliance with bupropion: a replication and extension study. Addict Behav. 2007 Apr;32(4):875-80.	X13
363	Morgenstern J, Morgan TJ, McCrady BS, Keller DS, Carroll KM. Manual-guided cognitive-behavioral therapy training: a promising method for disseminating empirically supported substance abuse treatments to the practice community. Psychol Addict Behav. 2001 Jun;15(2):83-8.	X12
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365	Morrison A, Wertheimer AI, Berger ML. Interventions to improve antihypertensive drug adherence: a quantitative review of trials (Structured abstract). Formulary. 2000;35(3):234-55.	X14
366	Morrow DG, Weiner M, Deer MM, Young JM, Dunn S, McGuire P, et al. Patient-centered instructions for medications prescribed for the treatment of heart failure. Am J Geriatr Pharmacother. 2004 Mar;2(1):44-52.	X5
367	Mugusi F, Mugusi S, Bakari M, Hejdemann B, Josiah R, Janabi M, et al. Enhancing adherence to antiretroviral therapy at the HIV clinic in resource constrained countries; the Tanzanian experience. Trop Med Int Health. 2009 Oct;14(10):1226-32.	X3
368	Mullan B, Snyder M, Lindgren B, Finkelstein SM, Hertz MI. Home monitoring for lung transplant candidates. Progress in transplantation (Aliso Viejo, Calif). 2003 Sep;13(3):176-82.	X1
369	Murphy DA, Lu MC, Martin D, Hoffman D, Marelich WD. Results of a pilot intervention trial to improve antiretroviral adherence among HIV-positive patients. J Assoc Nurses AIDS Care. 2002 Nov-Dec;13(6):57-69.	X8
370	Murphy JM, Mahoney MC, Cummings KM, Hyland AJ, Lawvere S. A randomized trial to promote pharmacotherapy use and smoking cessation in a Medicaid population (United States). Cancer Causes Control. 2005 May;16(4):373-82.	X1
371	Murray MD, Harris LE, Overhage JM, Zhou XH, Eckert GJ, Smith FE, et al. Failure of computerized treatment suggestions to improve health outcomes of outpatients with uncomplicated hypertension: results of a randomized controlled trial. Pharmacotherapy. 2004 Mar;24(3):324-37.	X1
372	Murray MD, Young JM, Morrow DG, Weiner M, Tu W, Hoke SC, et al. Methodology of an ongoing, randomized, controlled trial to improve drug use for elderly patients with chronic heart failure. Am J Geriatr Pharmacother. 2004 Mar;2(1):53-65.	X12
373	Muyingo SK, Walker AS, Reid A, Munderi P, Gibb DM, Ssali F, et al. Patterns of individual and population-level adherence to antiretroviral therapy and risk factors for poor adherence in the first year of the DART trial in Uganda and Zimbabwe. J Acquir Immune Defic Syndr. 2008 Aug 1;48(4):468-75.	X5
374	Naar-King S, Parsons JT, Murphy D, Kolmodin K, Harris DR. A multisite randomized trial of a motivational intervention targeting multiple risks in youth living with HIV: initial effects on motivation, self-efficacy, and depression. J Adolesc Health. 2010 May;46(5):422-8.	X1

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375	Naar-King S, Parsons JT, Murphy DA, Chen X, Harris DR, Belzer ME. Improving health outcomes for youth living with the human immunodeficiency virus: a multisite randomized trial of a motivational intervention targeting multiple risk behaviors. Arch Pediatr Adolesc Med. 2009 Dec;163(12):1092-8.	X1
376	Naber D, Lambert M. The CATIE and CUtLASS studies in schizophrenia: results and implications for clinicians. CNS Drugs. 2009 Aug 1;23(8):649-59.	X1
377	Narita M, Kellman M, Franchini DL, McMillan ME, Hollender ES, Ashkin D. Short-course rifamycin and pyrazinamide treatment for latent tuberculosis infection in patients with HIV infection: the 2-year experience of a comprehensive community-based program in Broward County, Florida. Chest. 2002 Oct;122(4):1292-8.	X4
378	Nazareth I, Burton A, Shulman S, Smith P, Haines A, Timberal H. A pharmacy discharge plan for hospitalized elderly patients--a randomized controlled trial. Age Ageing. 2001 Jan;30(1):33-40.	X3
379	Neugut AI, Subar M, Wilde ET, Stratton S, Brouse CH, Hillyer GC, et al. Association between prescription co-payment amount and compliance with adjuvant hormonal therapy in women with early-stage breast cancer. J Clin Oncol. 2011;29(18):2534-42.	X5
380	Niedermann K, Fransen J, Knols R, Uebelhart D. Gap between short- and long-term effects of patient education in rheumatoid arthritis patients: a systematic review (Provisional abstract). Arthritis and Rheumatism (Arthritis Care and Research). 2004(3):388-98.	X1
381	Nielsen D, Ryg J, Nielsen W, Knold B, Nissen N, Brixen K. Patient education in groups increases knowledge of osteoporosis and adherence to treatment: a two-year randomized controlled trial. Patient Educ Couns. 2010 Nov;81(2):155-60.	X3
382	Norman IJ, Coster S, McCrone P, Sibley A, Whittlesea C. A comparison of the clinical effectiveness and costs of mental health nurse supplementary prescribing and independent medical prescribing: a post-test control group study. BMC health services research. 2010;10:4.	X3
383	Nyamathi A, Nahid P, Berg J, Burrage J, Christiani A, Aqtash S, et al. Efficacy of nurse case-managed intervention for latent tuberculosis among homeless subsamples. Nurs Res. 2008 Jan-Feb;57(1):33-9.	X4
384	Nyamathi A, Stein JA, Schumann A, Tyler D. Latent variable assessment of outcomes in a nurse-managed intervention to increase latent tuberculosis treatment completion in homeless adults. Health Psychol. 2007 Jan;26(1):68-76.	X4
385	Nyamathi AM, Christiani A, Nahid P, Gregerson P, Leake B. A randomized controlled trial of two treatment programs for homeless adults with latent tuberculosis infection. Int J Tuberc Lung Dis. 2006 Jul;10(7):775-82.	X4
386	O'Connor PJ, Rush WA, Trence DL. Relative effectiveness of niacin and lovastatin for treatment of dyslipidemias in a health maintenance organization. J Fam Pract. 1997 May;44(5):462-7.	X1
387	Odegard PS, Gray SL. Barriers to medication adherence in poorly controlled diabetes mellitus. Diabetes Educ. 2008 Jul-Aug;34(4):692-7.	X5
388	O'Donnell C, Donohoe G, Sharkey L, Owens N, Migone M, Harries R, et al. Compliance therapy: a randomised controlled trial in schizophrenia. BMJ. 2003 Oct 11;327(7419):834.	X3
389	Ogedegbe G, Schoenthaler A. A systematic review of the effects of home blood pressure monitoring on medication adherence (Structured abstract). J Clin Hypertens. 2006(3):174-80.	X2
390	Ogedegbe G, Schoenthaler A, Richardson T, Lewis L, Belue R, Espinosa E, et al. An RCT of the effect of motivational interviewing on medication adherence in hypertensive African Americans: rationale and design. Contemporary clinical trials. 2007 Feb;28(2):169-81.	X12
391	Ollivier L, Romand O, Marimoutou C, Michel R, Pognant C, Todesco A, et al. Use of short message service (SMS) to improve malaria chemoprophylaxis compliance after returning from a malaria endemic area. Malaria journal. 2009;8:236.	X3
392	Olson KL, Delate T, Rasmussen J, Humphries TL, Merenich JA. Outcomes of patients discharged from pharmacy-managed cardiovascular disease management. Am J Manag Care. 2009 Aug;15(8):497-503.	X12
393	Olthoff CM, Schouten JS, van de Borne BW, Webers CA. Noncompliance with ocular hypotensive treatment in patients with glaucoma or ocular hypertension: an evidence-based review (Structured abstract). Ophthalmology 2004:953-61.	X5
394	Onyirimba F, Apter A, Reisine S, Litt M, McCusker C, Connors M, et al. Direct clinician-to-patient feedback discussion of inhaled steroid use: its effect on adherence. Ann Allergy Asthma Immunol. 2003 Apr;90(4):411-5.	X8

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395	Orton Lois C, Barnish G. Unit-dose packaged drugs for treating malaria. Cochrane Database of Systematic Reviews. 2005(2).	X4
396	Oslin DW, Lynch KG, Pettinati HM, Kampman KM, Gariti P, Gelfand L, et al. A placebo-controlled randomized clinical trial of naltrexone in the context of different levels of psychosocial intervention. Alcohol Clin Exp Res. 2008 Jul;32(7):1299-308.	X12
397	Oslin DW, Pettinati H, Volpicelli JR. Alcoholism treatment adherence: older age predicts better adherence and drinking outcomes. Am J Geriatr Psychiatry. 2002 Nov-Dec;10(6):740-7.	X7
398	Owen RR, Hudson T, Thrush C, Thapa P, Armitage T, Landes RD. The effectiveness of guideline implementation strategies on improving antipsychotic medication management for schizophrenia. Med Care. 2008 Jul;46(7):686-91.	X12
399	Owen-Smith A, Diclemente R, Wingood G. Complementary and alternative medicine use decreases adherence to HAART in HIV-positive women. AIDS Care. 2007 May;19(5):589-93.	X1
400	Pampallona S, Bollini P, Tibaldi G, Kupelnick B, Munizza C. Patient adherence in the treatment of depression (Structured abstract). Br J Psychiatry 2002:104-9.	X5
401	Pape GA, Hunt JS, Butler KL, Siemienczuk J, LeBlanc BH, Gillanders W, et al. Team-based care approach to cholesterol management in diabetes mellitus: two-year cluster randomized controlled trial. Arch Intern Med. 2011 Sep 12;171(16):1480-6.	X1
402	Parsons JT, Golub SA, Rosof E, Holder C. Motivational interviewing and cognitive-behavioral intervention to improve HIV medication adherence among hazardous drinkers: a randomized controlled trial. J Acquir Immune Defic Syndr. 2007 Dec 1;46(4):443-50.	X4
403	Parsons JT, Rosof E, Mustanski B. Medication adherence mediates the relationship between adherence self-efficacy and biological assessments of HIV health among those with alcohol use disorders. AIDS and behavior. 2008 Jan;12(1):95-103.	X13
404	Patel UB, Ni Q, Clayton C, Lam P, Parks J. An attempt to improve antipsychotic medication adherence by feedback of medication possession ratio scores to prescribers. Popul Health Manag. 2010 Oct;13(5):269-74.	X4
405	Patton K, Meyers J, Lewis BE. Enhancement of compliance among patients with hypertension. Am J Manag Care. 1997 Nov;3(11):1693-8.	X5
406	Paulos CP, Nygren CE, Celedon C, Carcamo CA. Impact of a pharmaceutical care program in a community pharmacy on patients with dyslipidemia. Ann Pharmacother. 2005 May;39(5):939-43.	X12
407	Peikes D, Chen A, Schore J, Brown R. Effects of care coordination on hospitalization, quality of care, and health care expenditures among Medicare beneficiaries: 15 randomized trials. JAMA. 2009 Feb 11;301(6):603-18.	X5
408	Pekkala Eila T, Merinder Lars B. Psychoeducation for schizophrenia. Cochrane Database of Systematic Reviews. 2002(2).	X4
409	Pencille LJ, Campbell ME, Van Houten HK, Shah ND, Mullan RJ, Swiglo BA, et al. Protocol for the Osteoporosis Choice trial. A pilot randomized trial of a decision aid in primary care practice. Trials. 2009;10:113.	X12
410	Perahia DG, Quail D, Gandhi P, Walker DJ, Peveler RC. A randomized, controlled trial of duloxetine alone vs. duloxetine plus a telephone intervention in the treatment of depression. J Affect Disord. 2008 May;108(1-2):33-41.	X3
411	Pereles L, Romonko L, Murzyn T, Hogan D, Silvius J, Stokes E, et al. Evaluation of a self-medication program. J Am Geriatr Soc. 1996 Feb;44(2):161-5.	X3
412	Petersen L, Jeppesen P, Thorup A, Abel MB, Ohlenschlaeger J, Christensen TO, et al. A randomised multicentre trial of integrated versus standard treatment for patients with a first episode of psychotic illness. BMJ. 2005 Sep 17;331(7517):602.	X4
413	Peters-Klimm F, Campbell S, Hermann K, Kunz CU, Muller-Tasch T, Szecsenyi J. Case management for patients with chronic systolic heart failure in primary care: the HICMan exploratory randomised controlled trial. Trials. 2010;11:56.	X1
414	Peterson AM, Takiya L, Finley R. Meta-analysis of trials of interventions to improve medication adherence (Structured abstract). Am J Health Syst Pharm. 2003(7):657-65.	X14
415	Peterson GM, Fitzmaurice KD, Naunton M, Vial JH, Stewart K, Krum H. Impact of pharmacist-conducted home visits on the outcomes of lipid-lowering drug therapy. J Clin Pharm Ther. 2004 Feb;29(1):23-30.	X3
416	Pettinati HM, Volpicelli JR, Pierce JD, Jr., O'Brien CP. Improving naltrexone response: an intervention for medical practitioners to enhance medication compliance in alcohol dependent patients. J Addict Dis. 2000;19(1):71-83.	X5

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417	Peveler R, George C, Kinmonth AL, Campbell M, Thompson C. Effect of antidepressant drug counselling and information leaflets on adherence to drug treatment in primary care: randomised controlled trial. BMJ. 1999 Sep 4;319(7210):612-5.	X3
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477	Schedlbauer A, Schroeder K, Fahey T. How can adherence to lipid-lowering medication be improved: a systematic review of randomized controlled trials (Brief record). Fam Pract. 2007(4):380-7.	X14
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481	Schnoll RA, Patterson F, Wileyto EP, Heitjan DF, Shields AE, Asch DA, et al. Effectiveness of extended-duration transdermal nicotine therapy: a randomized trial. Ann Intern Med. 2010 Feb 2;152(3):144-51.	X1
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490	Sedjo RL, Cox ER. The influence of targeted education on medication persistence and generic substitution among consumer-directed health care enrollees. Health Serv Res. 2009 Dec;44(6):2079-92.	X5
491	Sellwood W, Barrowclough C, Tarrier N, Quinn J, Mainwaring J, Lewis S. Needs-based cognitive-behavioural family intervention for carers of patients suffering from schizophrenia: 12-month follow-up. Acta Psychiatr Scand. 2001 Nov;104(5):346-55.	X4
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495	Sherrill JT, Frank E, Geary M, Stack JA, Reynolds CF, 3rd. Psychoeducational workshops for elderly patients with recurrent major depression and their families. Psychiatr Serv. 1997 Jan;48(1):76-81.	X5
496	Sikka R, Waters J, Moore W, Sutton DR, Herman WH, Aubert RE. Renal assessment practices and the effect of nurse case management of health maintenance organization patients with diabetes. Diabetes Care. 1999 Jan;22(1):1-6.	X12

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498	Simon GE, Katon W, Rutter C, VonKorff M, Lin E, Robinson P, et al. Impact of improved depression treatment in primary care on daily functioning and disability. Psychol Med. 1998 May;28(3):693-701.	X12
499	Simon GE, Katon WJ, VonKorff M, Unutzer J, Lin EH, Walker EA, et al. Cost-effectiveness of a collaborative care program for primary care patients with persistent depression. A J Psychiatry. 2001 Oct;158(10):1638-44.	X1
500	Simon GE, Ludman EJ, Bauer MS, Unutzer J, Operskalski B. Long-term effectiveness and cost of a systematic care program for bipolar disorder. Arch Gen Psychiatry. 2006 May;63(5):500-8.	X12
501	Simon GE, Manning WG, Katzelnick DJ, Pearson SD, Henk HJ, Helstad CS. Cost-effectiveness of systematic depression treatment for high utilizers of general medical care. Arch Gen Psychiatry. 2001 Feb;58(2):181-7.	X12
502	Simon GE, Ralston JD, Savarino J, Pabiniak C, Wentzel C, Operskalski BH. Randomized trial of depression follow-up care by online messaging. J Gen Intern Med. 2011;26(7):698-704.	X1
503	Simon JA, Lewiecki EM, Smith ME, Petruschke RA, Wang L, Palmisano JJ. Patient preference for once-weekly alendronate 70 mg versus once-daily alendronate 10 mg: a multicenter, randomized, open-label, crossover study. Clin Ther. 2002 Nov;24(11):1871-86.	X12
504	Simoni JM, Frick PA, Pantalone DW, Turner BJ. Antiretroviral adherence interventions: a review of current literature and ongoing studies. Top HIV Med. 2003 Nov-Dec;11(6):185-98.	X3
505	Simoni JM, Huh D, Frick PA, Pearson CR, Andrasik MP, Dunbar PJ, et al. Peer support and pager messaging to promote antiretroviral modifying therapy in Seattle: a randomized controlled trial. J Acquir Immune Defic Syndr. 2009 Dec 1;52(4):465-73.	X4
506	Sit JW, Yip VY, Ko SK, Gun AP, Lee JS. A quasi-experimental study on a community-based stroke prevention programme for clients with minor stroke. J Clin Nurs. 2007 Feb;16(2):272-81.	X3
507	Smith CE, Dauz E, Clements F, Werkowitch M, Whitman R. Patient education combined in a music and habit-forming intervention for adherence to continuous positive airway (CPAP) prescribed for sleep apnea. Patient Educ Couns. 2009 Feb;74(2):184-90.	X13
508	Smith SR, Rublein JC, Marcus C, Brock TP, Chesney MA. A medication self-management program to improve adherence to HIV therapy regimens. Patient Educ Couns. 2003 Jun;50(2):187-99.	X4
509	Smith-Rohrberg D, Mezger J, Walton M, Bruce RD, Altice FL. Impact of enhanced services on virologic outcomes in a directly administered antiretroviral therapy trial for HIV-infected drug users. J Acquir Immune Defic Syndr. 2006 Dec 1;43 Suppl 1:S48-53.	X12
510	Solari A, Martinelli V, Trojano M, Lugaresi A, Granella F, Giordano A, et al. An information aid for newly diagnosed multiple sclerosis patients improves disease knowledge and satisfaction with care. Mult Scler. 2010 Nov;16(11):1393-405.	X3
511	Solomon DH, Gleeson T, Iversen M, Avorn J, Brookhart MA, Lii J, et al. A blinded randomized controlled trial of motivational interviewing to improve adherence with osteoporosis medications: design of the OPTIMA trial. Osteoporos Int. 2010 Jan;21(1):137-44.	X12
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513	Solomon P, Draine J, Mannion E. The impact of individualized consultation and group workshop family education interventions in ill relative outcomes. J Nerv Ment Dis. 1996 Apr;184(4):252-5.	X13
514	Sommaruga M, Spanevello A, Migliori GB, Neri M, Callegari S, Majani G. The effects of a cognitive behavioural intervention in asthmatic patients. Monaldi Arch Chest Dis. 1995 Oct;50(5):398-402.	X12
515	Sookaneknun P, Richards RM, Sanguansermsri J, Teerasut C. Pharmacist involvement in primary care improves hypertensive patient clinical outcomes. Ann Pharmacother. 2004 Dec;38(12):2023-8.	X3

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517	Southard BH, Southard DR, Nuckolls J. Clinical trial of an Internet-based case management system for secondary prevention of heart disease. J Cardiopulm Rehabil. 2003 Sep-Oct;23(5):341-8.	X1
518	Sovani MP, Whale CI, Oborne J, Cooper S, Mortimer K, Ekstrom T, et al. Poor adherence with inhaled corticosteroids for asthma: can using a single inhaler containing budesonide and formoterol help? Br J Gen Pract. 2008 Jan;58(546):37-43.	X3
519	Spadaro A, De Luca T, Massimiani MP, Ceccarelli F, Riccieri V, Valesini G. Occupational therapy in ankylosing spondylitis: Short-term prospective study in patients treated with anti-TNF-alpha drugs. Joint Bone Spine. 2008 Jan;75(1):29-33.	X8
520	Spaniel F, Vohlidka P, Hrdlicka J, Kozeny J, Novak T, Motlova L, et al. ITAREPS: information technology aided relapse prevention programme in schizophrenia. Schizophr Res. 2008 Jan;98(1-3):312-7.	X5
521	Spiess K, Sachs G, Pietschmann P, Prager R. A program to reduce onset distress in unselected type I diabetic patients: effects on psychological variables and metabolic control. Eur J Endocrinol. 1995 May;132(5):580-6.	X8
522	Stant AD, Castelein S, Bruggeman R, van Busschbach JT, van der Gaag M, Knegtering H, et al. Economic aspects of peer support groups for psychosis. Community Ment Health J. 2011 Feb;47(1):99-105.	X12
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524	Stein MD, Solomon DA, Herman DS, Anthony JL, Ramsey SE, Anderson BJ, et al. Pharmacotherapy plus psychotherapy for treatment of depression in active injection drug users. Arch Gen Psychiatry. 2004 Feb;61(2):152-9.	X1
525	Stevens VJ, Shneidman RJ, Johnson RE, Boles M, Steele PE, Lee NL. Helicobacter pylori eradication in dyspeptic primary care patients: a randomized controlled trial of a pharmacy intervention. West J Med. 2002 Mar;176(2):92-6.	X13
526	Stewart A, Noakes T, Eales C, Shepard K, Becker P, Veriawa Y. Adherence to cardiovascular risk factor modification in patients with hypertension. Cardiovasc J S Afr. 2005 Mar-Apr;16(2):102-7.	X3
527	Stilley CS, Bender CM, Dunbar-Jacob J, Sereika S, Ryan CM. The impact of cognitive function on medication management: three studies. Health Psychol. 2010 Jan;29(1):50-5.	X1
528	Stringer JS, Sinkala M, Stout JP, Goldenberg RL, Acosta EP, Chapman V, et al. Comparison of two strategies for administering nevirapine to prevent perinatal HIV transmission in high-prevalence, resource-poor settings. J Acquir Immune Defic Syndr. 2003 Apr 15;32(5):506-13.	X13
529	Strinko JM, Di Bisceglie AM, Hoffmann JA. A descriptive study of the relationship between mood disorders and hepatitis C treatment compliance: does nursing play a role? Issues Ment Health Nurs. 2004 Oct-Nov;25(7):715-22.	X1
530	Strom O, Borgstrom F, Kanis JA, Jonsson B. Incorporating adherence into health economic modelling of osteoporosis. Osteoporos Int. 2009 Jan;20(1):23-34.	X1
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536	Swan GE, McClure JB, Jack LM, Zbikowski SM, Javitz HS, Catz SL, et al. Behavioral counseling and varenicline treatment for smoking cessation. Am J Prev Med. 2010 May;38(5):482-90.	X1

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537	Swanson AJ, Pantalon MV, Cohen KR. Motivational interviewing and treatment adherence among psychiatric and dually diagnosed patients. J Nerv Ment Dis. 1999 Oct;187(10):630-5.	X12
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	Study Information	Exclusion Code
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	Study Information	Exclusion Code
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	Study Information	Exclusion Code
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598	Webel AR. Testing a peer-based symptom management intervention for women living with HIV/AIDS. AIDS Care. 2010 Sep;22(9):1029-40.	X4
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609	Westling E, Garcia K, Mann T. Discovery of meaning and adherence to medications in HIV-infected women. J Health Psychol. 2007 Jul;12(4):627-35.	X4
610	Weycker D, Macarios D, Edelsberg J, Oster G. Compliance with drug therapy for postmenopausal osteoporosis. Osteoporos Int. 2006;17(11):1645-52.	X5
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	Study Information	Exclusion Code
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614	Williams A, Manias E, Walker R. Interventions to improve medication adherence in people with multiple chronic conditions: a systematic review. J Adv Nurs. 2008 Jul;63(2):132-43.	X14
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619	Wohl AR, Garland WH, Squires K, Witt M, Larsen R, Kovacs A, et al. The feasibility of a community-based directly administered antiretroviral therapy program. Clin Infect Dis. 2004 Jun 1;38 Suppl 5:S388-92.	X9
620	Wohl AR, Garland WH, Valencia R, Squires K, Witt MD, Kovacs A, et al. A randomized trial of directly administered antiretroviral therapy and adherence case management intervention. Clin Infect Dis. 2006 Jun 1;42(11):1619-27.	X4
621	Wong FK, Chow SK, Chan TM. Evaluation of a nurse-led disease management programme for chronic kidney disease: a randomized controlled trial. Int J Nurs Stud. 2010 Mar;47(3):268-78.	X3
622	Wu AW, Snyder CF, Huang IC, Skolasky R, McGruder HF, Celano SA, et al. A randomized trial of the impact of a programmable medication reminder device on quality of life in patients with AIDS. Aids Patient Care STDS. 2006 Nov;20(11):773-81.	X3
623	Wu JY, Leung WY, Chang S, Lee B, Zee B, Tong PC, et al. Effectiveness of telephone counselling by a pharmacist in reducing mortality in patients receiving polypharmacy: randomised controlled trial. BMJ. 2006 Sep 9;333(7567):522.	X3
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625	Wysocki T, Greco P, Harris MA, Bubb J, White NH. Behavior therapy for families of adolescents with diabetes: maintenance of treatment effects. Diabetes Care. 2001 Mar;24(3):441-6.	X13
626	Yazaki Y, Faridi Z, Ma Y, Ali A, Northrup V, Njike VY, et al. A pilot study of chromium picolinate for weight loss. J Altern Complement Med. 2010 Mar;16(3):291-9.	X1
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629	Zarani F, Besharat MA, Sadeghian S, Sarami G. The effectiveness of the information-motivation-behavioral skills model in promoting adherence in CABG patients. J Health Psychol. 2010 Sep;15(6):828-37.	X12
630	Zeber JE, Grazier KL, Valenstein M, Blow FC, Lantz PM. Effect of a medication copayment increase in veterans with schizophrenia. Am J Manag Care. 2007 Jun;13(6 Pt 2):335-46.	X4
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632	Ziller V, Kalder M, Albert US, Holzhauer W, Ziller M, Wagner U, et al. Adherence to adjuvant endocrine therapy in postmenopausal women with breast cancer. Ann Oncol. 2009 Mar;20(3):431-6.	X2

	Study Information	Exclusion Code
633	Znoj HJ, Messerli-Burgy N, Tschopp S, Weber R, Christen L, Christen S, et al. Psychotherapeutic process of cognitive-behavioral intervention in HIV-infected persons: results from a controlled, randomized prospective clinical trial. Psychother Res. 2010 Mar;20(2):203-13.	X4
634	Zweben A, Pettinati HM, Weiss RD, Youngblood M, Cox CE, Mattson ME, et al. Relationship between medication adherence and treatment outcomes: the COMBINE study. Alcohol Clin Exp Res. 2008 Sep;32(9):1661-9.	X4
635	Implementation of treatment protocols in the Diabetes Control and Complications Trial. Diabetes Care. 1995 Mar;18(3):361-76.	X1
636	Testing combined pharmacotherapies and behavioral interventions for alcohol dependence (the COMBINE study): a pilot feasibility study. Alcohol Clin Exp Res. 2003 Jul;27(7):1123-31.	X13
637	Abrahams N, Jewkes R, Lombard C, Mathews S, Campbell J, Meel B. Impact of telephonic psycho-social support on adherence to post-exposure prophylaxis (PEP) after rape. AIDS Care. 2010 Oct;22(10):1173-81.	X3

Appendix D. Comprehensive Evidence Tables

Abbreviations

95% CI	95% confidence interval
AA(s)	African-American(s)
ACE	Angiotensin-converting enzyme
AD	Antidepressant
Adj	Adjusted
ANCOVA	Analysis of covariance
aOR	Adjusted odds ratio
Approx	Approximately
Appt(s)	Appointment(s)
ARB	Angiotensin receptor blockers
Avg	Average
BL	Baseline
BP	Blood pressure
CAD	Coronary artery disease
CBT	Cognitive behavioral therapy
Chi-sq	Chi-square value
CO	Colorado (Table 1B)
Col	Column
Cont'd	Continued
Couns	Counseling
DBP	Diastolic blood pressure
Diff	Difference
Dl	Deciliter(s)
Dx	Diagnosis
Dz(s)	Disease(s)
ED	Emergency Department
Educ	Education/Educational
EP	Endpoint
Gov't	Government
HbA1C or HA1C	Hemoglobin A1C
HF	Heart failure
Hg	Mercury
HIV	Human immunodeficiency virus
HMO(s)	Health maintenance organization(s)
HR(s)	Hazards ratio(s)
Hr(s)	Hour(s)
HTN	Hypertension
ICS	Inhaled Corticosteroid
Info	Information
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
MD(s)	Medical doctor(s)/Physician(s)

MEMS	Micro-Electro-Mechanical Systems
Mg(s)	Milligram(s)
MI	Myocardial infarction
Mm(s)	Millimeter(s)
Mo(s)	Month(s)
NA	Not applicable
NP(s)	Nurse practitioner(s)
NR, N-RNR	Not reported
NS	Not significant or Not specified
OR	Odds ratio
PA(s)	Physician assistant
PCP(s)	Primary care provider(s)
Pharma	Pharmaceutical
PRD	Pharmacy refill data
PRN	When necessary (from P.R.N., Latin for “pro re nata”)
RCT	Randomized controlled trial
RN(s)	Registered nurse(s)
RR	Risk ratio
Rx(s)	Prescription(s)
SBP	Systolic blood pressure
SCL	Symptom Checklist Depression scale
SCr	Serum creatinine
SD	Standard deviation
SE	Standard error
SG1, SG2,…SGN	Subgroup 1, 2,…N
T1, T2,…TN	Time 1, 2,…N
VA	Veterans Administration
Vs.	Versus
Wk(s)	Week(s)
Yr(s)	Year(s)

Table D1. Description of intervention and comparison groups

Author, Year Trial name	Groups	Interventions and Comparators	Medication Name(s)/ Class(es)/Indication(s)
Bender et a., 2010[1] NA	G1: Interactive voice response (IVR) intervention G2: Usual care	G1: Each patient received at least two IVR calls separated by 1 month; veri fied correct person had been called; if respondent indicated that during the previous week awoken at night, limited activities, or use of rescue inhaler >2 times, then told that daily use of controller meds should prevent symptoms; advised to discuss symptoms with physician. Modules on benefits of asthma meds and filling and using meds provided with tailored responses; participants informed about free telephone service to answer asthma questions and free smoking cessation phone line; participants who reported symptoms or no intention of refilling meds received a 3rd IVR call 2 weeks following call #2. G2: usual care; not described	ICS
Berg et al., 1997[2] NA	G1: Self-management intervention G2: Usual care	G1: 6 sessions provide info about self-management behaviors and skills, asthma medications, asthma triggers, prevention of asthma attacks, relaxation techniques, psychological responses to asthma, and problem-solving skills. The session last approx 2 hours, led by registered nurse. All info was scripted in handbook for group leaders G2: Recorded information daily for 1 week following randomization and again at follow-up for treated subjects. No other intervention was given to this group aside from usual care with physician.	Asthma
Berger et al., 2005[3] NA	G1: Software-based telephone counseling intervention G2: Control arm	G1: 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 - based counseling sessions. G2: Did not receive calls, but had access to Call Center staff via standard toll-free hotline mechanisms.	Avonex/Multiple Sclerosis Medication
Bogner et al., 2008[4] NA	G1: Integrated care G2: Usual care	G1: For patient, the integrated care manager provided education about depression and hypertension, emphasizing the control of depression to manage hypertension; offered encouragement and relief from stigma; helped to identify target symptoms for both conditions; explained the rationale for antidepressant and antihypertensive medication usage; assessed for side-effects and assisted in their management; assessed progress (e.g., reduction in depressive symptoms); assisted with referrals; and monitored and responded to life-threatening symptoms (e.g., chest pain, suicidality - 3, 30-minute in-person sessions and 2, 15-minute telephone-monitoring contacts during a 4-week period. G2: Usual care participants underwent the same assessments as participants in the integrated care intervention; no other differences mentioned	Depression, hypertension meds

Table D1. Description of intervention and comparison groups (continued)

Author, Year Trial name	Groups	Interventions and Comparators	Medication Name(s)/ Class(es)/Indication(s)
Bogner et al., 2010[5] NA	G1: Integrated care G2: Usual care	G1: Integrated care intervention that addresses each factor resulting in non-adherence in a conceptual model adapted from Cooper and colleagues (source 33) through a multifaceted, culturally tailored individualized approach in which participants work with an integrated care manager to develop strategies to overcome barriers to medication adherence. The intervention integrates depression treatment with care for diabetes. G2: Usual care - existing primary care treatment	Oral hypoglycemics, antidepressants
Bosworth et al., 2005[6] V-STITCH	G1: Nurse administered intervention G2: Usual care	G1: Calls every 2 months for 24 months delivered by a nurse with research experience; at each call, nurse delivers both tailored and standard information in nine modules: literacy, hypertension knowledge, memory, social support, patient/provider communication, medication refills, missed appointments, health behaviors, and side effects. The activation frequency of each module can vary. To ensure that tailored information is standardized, the nurse uses a computerized database, which contains pre-determined scripts and tailoring algorithms. The database also tracks information discussed at each phone call. Duration of each call is recorded and database informs the nurse when the patient needs to be called again and what transpired during past phone conversations. Patients are also able to telephone nurse with questions related to hypertension. G2: No other contact other than completing measures at baseline and follow-up. BP measurements obtained from medical records. No alterations to usual care.	Anti-hypertensive medications
Bosworth et al., 2008[7] TCYB Bosworth et al., 2007[8] TCYB Methods paper	G1: Behavioral intervention G2: Usual care	G1: Nurse conducted telephone encounters every 8 weeks where a core group of modules is potentially activated. Each call begins with the medication module where patients are queried about hypertension medication regimen (i.e., understanding the purpose of medication) and adherence to guidelines (i.e., assessing for changes to regimen). Nurse offers to give friend or family member overview of medication regimen. The adverse effects module is also activated at every call. Additional modules include memory, knowledge/risk perception, participatory decision-making, social support, knowledge, literacy, and health behaviors (i.e., smoking, weight loss, diet, etc.) are activated at specific telephone encounters. Calls are tailored to each specific patient. At end of each call, nurse asks patient for BP measurement. Patients are also allowed to call the nurse if they had any concerns regarding HTN treatment. G2: No contact by nurse, no change in care	Antihypertensive drugs

Table D1. Description of intervention and comparison groups (continued)

Author, Year Trial name	Groups	Interventions and Comparators	Medication Name(s)/ Class(es)/Indication(s)
Capoccia et al., 2004[9] na	G1: Pharmacist - primary care intervention: Enhanced care G2: Usual Care	G1: In addition to UC, received follow-up by clinical pharmacist or pharmacy resident with the PCP and study psychiatrist. F-U was weekly phone calls for the first 4 weeks followed by phone contact every 2 weeks through week 12. During months 4–12, subjects received a phone call every other month. Subjects encouraged to visit their PCP during weeks 4 and 12. At each contact, depressive symptoms and medication-related concerns addressed by pharmacist. The initial contacts focused on support and education, medication dosage adjustment and the management of adverse effects. Med refill authorizations were provided, and access to patient assistance programs was facilitated. Also included change in time of dose administrations, change or discontinuation of AD meds, and provision of additional pharmacotherapy for insomnia or sexual dysfunction, as needed. Appts with MH providers also facilitated G2: Encouraged to use available resources (PCPs, pharmacists, nurses, andmental health providers)	Depression
Carter et al., 2009[10] NA	G1: Intervention G2: Control	G1: Physician/clinical pharmacist collaborative model identical to intervention used in previous study (Carter #2345) G2: Patients received BP measurements at baseline, 3 and 6 months. Clinical pharmacists abstained from providing care to patients in control group.	Antihypertensive medications
Chernew et al., 2008[11] NA	G1: Received a decrease in copayments G2: Copayments remained the same	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	(ACE inhibitors, ARBs, beta-blockers, diabetes medications (oral and insulin), HMG-CoA reductase inhibitors (statins), and inhaled corticosteroids
Choudhry et al., 2010[12] NA	G1: Intervention, Statins G2: Intervention, clopidogrel G3: No change in copayments, statin users G4: No change in copays clopidogrel users	G1: Elimination of copayments for statins for company employees & beneficiaries with diabetes or vascular disease. Pitney Bowes G2: Lowered copayments for all employees & beneficiaries prescribed clopidogrel. Pitney Bowes G3: No change in copayments, statin users. BCBS of NJG4: No change in copay, clopidogrel users. BCBS of NJ	Statins, clopidogrel
Choudhry et al., 2011[13] MI FREEE	G1: Full prescription coverage G2: Usual prescription coverage	G1: Patients had no cost sharing for any brand-name or generic statin, beta-blocker, ACE inhibitor, or ARB prescription after randomization. All copayments and coinsurance were waived at the pharmacy, as was any contribution to deductible. G2: Patients received their usual level of prescription-drug coverate	Statins, beta-blockers, ACE inhibitors, and ARBs

Table D1. Description of intervention and comparison groups (continued)

Author, Year Trial name	Groups	Interventions and Comparators	Medication Name(s)/ Class(es)/Indication(s)
Friedman et al., 1996[14] NA	G1: Patients who received telephone-linked computer system and regular medical care G2: Patients who received regular medical care alone	G1: Telephone-linked computer system - an interactive computer-based telecommunications system that converses with patients in their homes between office visits to their physicians. A supplement to usual care. TLC uses computer-controlled speech and touch tone keypad for responses. The systems ask about clinical status and gives feedback to the patient to promote adherence to treatments. G2: Regular medical care (not described)	Antihypertensives
Fulmer et al., 1999[15] NA	G1: Videotelephone reminder group G2: Telephone reminder group G3: Control group	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.	ACE inhibitors, calcium channel blockers, and other cardiac-related medications such as digoxin, diuretics, and vasodilators
Grant et al., 2003[16] NA	G1: Pharmacist-administered questionnaire and education physician feedback G2: Pharmacist-administered questionnaire only	G1: Six over the phone pharmacist-administered tasks: 1) a 13-item questionnaire to assess barriers to adherence to medications, diet, exercise; 2) detailed assessment of medication-specific regimen, use and barriers for each medication taken; 3) tailored verbal patient education based on barriers identified; 4) social service and nutrition referrals as needed; 5) email summary of barriers to physician; 6) offer in email summary to schedule follow up physician or pharmacist appointment. G2: Over the phone pharmacist-administered 13-item questionnaire to assess barriers to adherence to meds, diet, exercise; G3: set aside lab controls	Any diabetes-related medicines
Guthrie et al., 2001[17] First Myocardial Infarction (MI) Risk Reduction Program	G1: Postal and telephone reminders G2: Usual care	G1: Received first 2-week supply of pravastatin free of charge; received from physician life style recommendations and complying with medication regimen; Received telephone reminders at weeks 2 and 8 and reminder postcards at week 4 to reinforce message about coronary risk reduction; each message stressed importance of following physicians' instructions and taking medications as prescribed; reminder cards mailed at 4 and 5 months after enrollment also G2: Received first 2-week supply of pravastatin free of charge; received from physician life style recommendations and complying with medication regimen; reminder cards mailed only 4 and 5 months after enrollment;	Pravastatin
Hoffman et al., 2003[18] NA	G1: Mail-based intervention for providers and patients G2: Usual care	G1: Prescribers received letters each month listing their patients taking antidepressant drugs who were identified as nonadherent through pharmacy database claims. Patients identified as nonadherent received an intervention letter with general information reminding them of the importance of adhering to their medication regimen. G2: Usual care	Antidepressant medications

Table D1. Description of intervention and comparison groups (continued)

Author, Year Trial name	Groups	Interventions and Comparators	Medication Name(s)/ Class(es)/Indication(s)
Hunt et al., 2008[19] NA	G1: Collaborative primary care-pharmacist hypertension management G2: Usual care	G1: Scheduled for an appointment in primary care clinic with a Network-employed pharmacy practitioner. Pharmacists reviewed subjects' medications and lifestyle habits, assessed vital signs, screened for adverse drug reactions, identified barriers to adherence, provided education, optimized the antihypertensive regimen, and scheduled follow up appointments if necessary. G2: Normal schedule of medical care	Antihypertensives
Janson et al., 2003[20] NA	G1: Self-management education G2: Usual Care	G1: Included asthma education components recommended by NIH guidelines: Basic facts about asthma, role of airway inflammation and bronchospasm in causing airflow obstruction and symptoms, and the roles and actions of anti-inflammatory and quick relief medications were explained with models and illustrations. Skills for correct inhalation of medication from a metered-dose inhaler using a spacer and for peak flow measurement were taught and practiced. At subsequent visits, subjects were shown graphs of their peak flow data, emphasizing trends over time. Finally, a simple written asthma action plan, based on peak flow zones, and using the "traffic light" analogy G2: Monitored peak flow, symptoms, and medication use, and had the same number of study visits of the same duration. No explicit education or instruction aboutasthma, and no feedback about peak flow data, symptoms, or medication adherence. All questions aboutasthma referred to the subject's personal physician	Asthma medications: Inhaled corticosteroids, albuterol
Janson et al., 2009[21] NA	G1: Individualized self-management educational intervention G2: Self-monitoring alone	G1: Standardized components regarding asthma facts and medication actions, as well as individualized components: verbal and graphic interpretation of spirometric results, peak flow trends, metered dose inhaler technique errors, and results of allergen skin testing, along with specific strategies for control of personally relevant environmental exposures. Peak flow monitor of the intervention participants was adjusted to reveal how daily readings compared with individual personal best values. Zones based on a ''traffic light'' analogy were displayed on the monitor face and correlated to a simple written action plan. The action plan was not personalized G2: Self-monitoring alone.	(ICS

Table D1. Description of intervention and comparison groups (continued)

Author, Year Trial name	Groups	Interventions and Comparators	Medication Name(s)/ Class(es)/Indication(s)
Johnson et al., 2006[22] NR	G1: Pro-Change Program for Cholesterol Medication G2: Control	G1: Based on transtheoretical model (TTM) for change; a computer-generated, individualized, stage-matched expert system intervention and stage-matched manual for adherence to lipid lowering medication. At baseline, expert system provides feedback on how a participant's responses compare to the responses of a sample of successful individuals making the same behavior change (normative feedback) for each TTM construct. At follow-up, the system provided printed intervention reports with normative and its own previous responses for each of the TTM constructs. Feedback is compiled into a single 4-5 page report mailed within 1 week of assessment. Feedback also refers participant to the self-help manual for adherence organized by stages of change which provides more in-depth information and stage-matched exercises. Feedback report also contains brief stage-matched guidance regarding stage of change for moderate exercise and dietary fat reduction. G2: Did not receive intervention materials	Lipid medications
Johnson et al., 2006[23] NR	G1: Pro-Change Program for High BP Medication G2: Control	G1: based on transtheoretical model for change; a computer-generated, individualized, stage-matched expert system intervention and stage-matched manual for adherence to antihypertensives. At baseline, expert system provided normative (compared to others) printed intervention reports based on response to baseline assessment. At follow-up, system provided printed intervention reports with normative and ipsative (compared to self) feedback on stages of change; decisional balance; processes of change (POC); self- efficacy; and strategies. The self-help manual reinforced principles and POC that were most appropriate for individual's current stage of change. Manual contains stage-matched exercises to help participant better understand and make use of behavioral strategies suggested in report. These materials were mailed to participants during assessment periods. G2: NR	Anti-hypertensive medications
Katon et al., 1995[24] NA	G1: Collaborative care G2: Usual care	G1: Prior to PCP visit, patients received 2 brief booklets (one on biology of depression and how antidepressants work, and one on CBT techniques for managing depression) and a videotape with similar material covered in doctor-patient vignettes. They also completed a doctor-patient questionnaire to bring to their first PCP visit. Physicians had a half-day didactic on depression treatment, monthly case conferences, and case-by-case consultation with study psychiatrists. Patients had 2 psychiatric visits--psychiatrist provided education to patients about antidepressant treatment and worked with PCPs to change dosage when needed. Psychiatrist monitored pharmacy refill data and notified PCP about premature discontinuation. G2: Patients received treatment for depression from their PCP, and could refer themselves or be referred to a mental health clinic.	Anti-depressant medication

Table D1. Description of intervention and comparison groups (continued)

Author, Year Trial name	Groups	Interventions and Comparators	Medication Name(s)/ Class(es)/Indication(s)
Katon et al., 1996[25] NA	G1: Collaborative care (intervention) G2: Usual care by primary care physicians (control)	G1: A multifaceted structured intervention targeting the patient, physician, and process of care. This included a collaborative model of care provided by both a primary care physician and 1 of the 2 study psychologists and included both behavioral treatment to manage depression and counseling to improve adherence. Patients also received a brief booklet on the biology of depression and how antidepressant medications work and another booklet on simple cognitive behavior techniques for managing depression and a 20-minute video tape to take home and view with their spouses. G2: Patients received treatment for depression from their primary care physician. This usually included prescription of an antidepressant, 2 to 3 visits over the first 3 months of treatment, and the option to refer to mental health services.	Antidepressant medications
Katon et al., 1999[26] NA Katon et al., 2002[27] NA	G1: Depression persistence intervention G2: Usual care	G1: Multifaceted intervention targeting patients, physicians, and process of care; Patients received education (book & videotape); 2 scheduled visits with a psychiatrist and additional visits as needed; brief telephone calls between visits; psychiatrist helped primary care provider and patient adjust dosages/medication when side effects or inadequate response to treatment occurred; PCPs received immediate updates about their patient's progress. G2: Usual care; typically prescription of an antidepressant medication, 2-3 visits over the first 6 months of treatment, and an option to refer to mental health services.	Antidepressant medications
Katon et al., 2001[28] NA Ludman et al., 2003[29] NA Van Korff et al., 2003[30] NA	G1: Depression relapse prevention program G2: Usual care	G1: Intervention patient educated about effective management of chronic/recurrent depression (included a book and videotape); had 2 in-person visits with a depression prevention specialist; contacted by telephone (3 times) and personalized mailings (4 times) for continued monitoring of depressive symptoms and patient adherence; cognitive behavioral components (stand-alone interventions; stress reduction; self-monitoring; tracking of symptoms; self-care plans. Depression prevention specialists communicated with PCP regarding situations requiring clinical attention. G2: Usual care; typically a prescription of an antidepressant medication, 2 to 4 visits over the first 6 months of treatment, and an option to refer to mental health services.	Antidepressant medications

Table D1. Description of intervention and comparison groups (continued)

Author, Year Trial name	Groups	Interventions and Comparators	Medication Name(s)/ Class(es)/Indication(s)
Lee et al., 2006[31] FAME	G1: Pharmacy care program G2: Usual care	G1: All received intervention during phase 1 prospective observational phase. Contained 3 elements: individualized medication education (using standardized scripts teaching drug names, indications, strengths, adverse effects, and usage instructions); medications dispensed using an adherence aid (blister packs); and regular follow-up with clinical pharmacists every 2 months. Initial visit was 1 hour, subsequent visits scheduled for 30 minutes. After conclusion of phase 1, continued to meet with clinical pharmacist every 2 months, continued to receive medications in blister packs, and continued mediation education as needed. G2: Returning to pre-study status of medication provision after conclusion of phase 1; medication education and blister-packed medications not provided; in phase 2, all medications provided in new pill bottles with a 90-day supply and 1 refill prescription	Multiple, not specified (4 or more meds)
Lin et al., 2006[32] NA	G1: Individualized management of depression G2: Consult primary care physician	G1: Individualized management of depression care according to patient preference and treatment response, using one of 2 evidence-based treatments: antidepressant medication or problem-solving treatment; Involved a stepped care approach that augmented pharmacotherapy, problem-solving treatment, or both with psychiatric consultations and group and community services G2: Advised to consult their primary care physician regarding depression treatment	Oral hypoglycemic agents, antihypertensive agents, and lipid-lowering medications
Maciejewski et al., 2010[33] NA	G1: BCBS North Carolina Value-based insurance design G2: Nonparticipants	G1: Generic copayments waived only for Blue Cross Blue Shield of North Carolina (BCBSNC) participants in value-based insurance program; in addition, copayments for brand-name medications to treat diabetes, hypertension, hyperlipidemia, and congestive heart failure lowered from tier 3 to tier 2 for all of the insurer's enrollees G2: No reductions in generic copayments; copayments for brand-name medications to treat diabetes, hypertension, hyperlipidemia, and congestive heart failure lowered from tier 3 to tier 2 for all of the insurer's enrollees	Medications for diabetes, hypertension, hyperlipidemia, and congestive heart failure
Mann et al., 2010[34] The Statin Choice	G1: Statin Choice Decision Aid G2: American Diabetes Association (ADA) print material	G1: 6 min provider-led discussion of patient's tailored risks and benefits from using or not a statin. Uses Statin Choice Decision Tool to complete 4 discrete steps: 1) discuss patient's underlying heart attack risk factors; 2) discuss patient's risk of heart attack over 10 yrs with and without statin; review risks of taking statin; 4) offer choices. Received one of three versions depending on which of three risk categories they were in: <15%; 15-30%; >30%. Risk determined using data from med records. G2: Printed material from ADA about how to reduce cholesterol through dietary modifications	Statins

Table D1. Description of intervention and comparison groups (continued)

Author, Year Trial name	Groups	Interventions and Comparators	Medication Name(s)/ Class(es)/Indication(s)
Montori et al., 2011[35] NA	G1: Intervention G2: Control	G1: Intervention patients received a decision aid (a tailored pictographic 10-year fracture risk estimate, absolute risk reduction with bisphosphonates, side effects, and out-of-pocket cost) in addition to usual care (review of bone mineral density results without fracture risk calculation or graphic representation of treatment benefit) G2: Control patients received a standard brochure in addition to usual care	Biphosphonate
Murray et al., 2007[36] NA	G1: Pharmacist-led intervention G2: Usual Care	G1: Pharmacist-led intervention providing patient-centered verbal instructions and written materials (literacy sensitive) about meds, icons on medication bottles/lids, monitoring of medication use. The pharmacist contacted clinicians as needed and was trained by a multidisciplinary team. G2: Received prescriptions from pharmacists (these pharmacist did not receive specialized training from multidisciplinary team) who rotated through study pharmacy but didn't have access to pt-centered study materials. No contact with intervention pharmacist other than initial medication history.	Multiple HF meds (median of 10-11)
Nietert et al., 2009[37] NA	G1: "Phone Patient" Intervention G2: "Fax Physician" Intervention G3: Usual care	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 = filling prescriptions when requested by patients and arranging payment	Medications for any 1 of 6 chronic diseases
Okeke et al., 2009[38] N-A	G1: Intervention G2: Usual care	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 1st 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.	Glaucoma medication--travoprost (prostaglandin analog)

Table D1. Description of intervention and comparison groups (continued)

Author, Year Trial name	Groups	Interventions and Comparators	Medication Name(s)/ Class(es)/Indication(s)
Pearce et al., 2008[39] Cardiovascular Risk Education and Social Support (CaRESS) Trial	G1: 50 G2 (intervention group B): 58 G3: 91	G1: An intervention that fostered the involvement of a relative or friend as a support person in the control of cardiovascular risk factors in patients with type 2 diabetes. It consisted of one patient/support person education session with a Registered Nurse patient educator with attendance of the support person followed by the mailing of 4 quarterly "newsletters" about cardiovascular risk factor control. G2: Same as G1 G3: An individual patient education session with a Registered Nurse patient educator, followed by the same 4 quarterly patient newsletters as sent to intervention group patients, but without formal involvement of a support person in the study.	Antidiabetic medications
Powell et al., 1995[40] NA	G1: Intervention G2: Control	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, & why adherence is important G2: Received no educational materials	Benazepril, metoprolol, simvastatin, transdermal estrogen
Powers et al., 2011{Powers, 2011 #13813 NA	G1: personalized risk-communication G2: risk factor education control group	G1: received standard risk factor education and information based on their personal Framingham CHD and stroke risk score; personalized information was presented verbally and in graphic form representing the patient's risks; average and optimal CHD and stroke risks based on published estimates for their 5- year age group also presented in graphical form with their estimated risk; presented with potential strategies to improve their risk through risk factor modification such as medication and patient lifestyle factors. A copy of the patient's personal risk information was also provided to the primary care provider. G2: received written patient education materials from the American Heart Association/American Stroke Association entitled “Are You at Risk of Heart Attack or Stroke?” which reviewed risk factors and how these factors can be improved but did not provide personalized estimates of individual risk; a research assistant verbally reviewed the information s and answered any questions at the initial visit.	NR
Pyne et al., 2011[41] HIV Translating Initiatives for Depression Into Effective Solutions (HITIDES)	G1: Collaborative care G2: Usual care	G1: Collaborative care model with HIV and mental health clinicians; included participant education and activation, assessment of treatment barriers and possible resolutions, depression symptoms and treatment monitoring, substance abuse monitoring, and instruction in self-management; intervention used 5-step stepped care model: watchful waiting, (2) depression care team treatment suggestions (counseling or pharmacotherapy, considering participant preference), (3) pharmacotherapy suggestions after review of depression treatment history by the clinical pharmacist, (4) combination pharmacotherapy and specialty mental health counseling, and (5) referral to specialty mental health. Study team communicated with clinicians via electronic medical records and with patients via phone. G2: HIV health care providers received 1 hour of HIV and depression training. Patients were screened for depression at baseline and delivered results to HIV clinicians at most clinic visits	Antidepressant medications, HIV medications

Table D1. Description of intervention and comparison groups (continued)

Author, Year Trial name	Groups	Interventions and Comparators	Medication Name(s)/ Class(es)/Indication(s)
Rich et al., 1996[42] NA	G1: Multidisciplinary intervention G2: Usual care	G1: Received comprehensive teaching about congestive heart failure and its management using a 15-page teaching guide prepared by study team; patients seen daily by study nurse through remainder of hospital stay; importance of compliance with medications and diet emphasized repeatedly; seen by a registered dietician and a social services representative; shortly before discharge, geriatric cardiologist reviewed patient's medications and made specific recommendations to simplify and consolidate a regimen by minimizing both the number of medications and dosing frequently; final choice of medications was decided by PCP; following discharge, patient seen by hospital's homecare department and regularly contacted by study nurse G2: Received conventional care under discretion of regular physician; received all standard hospital services, including teaching and pre-discharge medication instructions.	Various HF medications
Rickles et al., 2005[43] NA	G1: Pharmacist-guided education and monitoring (PGEM) G2: Usual care	G1: Pts. received 3 calls, baseline and at 1 and 2 mos; 1st: assessed the patient's AD med knowledge and beliefs, adverse effects and other concerns, treatment goals or areas in which they hoped the medication would help, and how the medication was being used during the week before the telephone call. Study pharmacists probed, provided education, asked patients to rate the severity of their concerns, and made recommendations on how to handle any adverse effects, difficulties remembering or paying for medications, and other concerns. Pharmacists expected to follow up on any indication of medication non-adherence. For calls 2 and 3, study pharmacists used the monitoring tool to guide their follow-up on any issues or concerns identified in earlier calls; also reviewed current adherence, whether any new adverse effects and concerns had developed, and progress in pts' medication goals. The pharmacist made new recommendations to patients as needed. G2: Educ and monitoring typical at the study pharmacies.	Depression
Ross et al., 2004[44] NR	G1: Online medical record access G2: Control	G1: Participants given user name and password to SPPARO online medical record site and received a user guide for the system; SPPARO contains medical record (clinical notes, laboratory reports, and test results), an educational guide (online version of printed materials all patients in heart failure practice receive at first visit), and a messaging system (allowed patients to exchange secure messages with the nursing staff). G2: Continued to receive standard care; offered use of SPPARO after study was completed as incentive to participate	Various

Table D1. Description of intervention and comparison groups (continued)

Author, Year Trial name	Groups	Interventions and Comparators	Medication Name(s)/ Class(es)/Indication(s)
Rudd et al., 2004[45] NA	G1: Usual care + nurse care management G2: Usual care only	G1: At baseline, nurse counseled on correct use of automated BP device, regular return of the automatically printed BP reports, tips for enhancing drug adherence, and recognizing potential drug side effects; printed materials extended this instruction and patients confirmed ability to use BP device; nurse initiated follow-up phone contacts at 1 week, and 1,2, and 4 months; during each call, nurse asked about each medication dosage and any problems experience since previous contact; encouraged patients to telephone anytime during regular hours with questions or concerns; contacted physicians to obtain permission to initiate any new BP drug but not any changes in dosage; medication adjustments made according to patient's current medications, lab values, and BP measurements; when 80% of home BP readings met goal of 130/85, no further changes made to therapy; when <80% home BP readings met goal, nurse increased drug dosage to max level recommended for each drug or added drugs according to protocol G2: NR	Anti-hypertensive medications
Rudd et al., 2009[46] NA	G1: Individualized Care Group (and Plain English Material Group) G2: Standard Care Group	G1: Individualized Care received standard rheumatology care; a notebook containing Arthritis Foundation pamphlets written in plain language (5-8th grade on SMOG), examples of medicine calendars, and a map of the hospital; and 2 appointments with a health educator, each after a rheumatology appointment. Originally there were 2 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.	Arthritis medications (not specified)
Schaffer et al., 2004[47] NA	G1: Audio-tape and education brochure G2: Audio-tape only G3: Brochure only G4: Standard provider education	G1: “Bob’s Lung Story” (Lelko, 1999) is a 30-minute audiotape w/ five NAEPP topics. The storyline repeatedly incorporates key components of PMT (vulnerability, severity, self-efficacy, and response efficacy), as substantiated by a published protection motivation theorist and models the development of protection motivation (adherence behavior) as the protagonist, Bob, moves through an acute asthma episode, diagnosis, confusion with medication use, and finally mastery of his asthma symptoms through medication adherence. Asthma-related lyrics set to popular tunes enhance memory, while emphasizing key points of asthma management. Plus book (described in G3) G2: Tape only. G3: Book only: 12-page booklet that covers the same NHLBI-recommended topics as the audiotape but does not presents as part of a larger narrative. G4: Whatever education was provided by the participant’s asthma care provider	Asthma

Table D1. Description of intervention and comparison groups (continued)

Author, Year Trial name	Groups	Interventions and Comparators	Medication Name(s)/ Class(es)/Indication(s)
Schectman et al., 1994[48] NA	G1: Telephone contact G2: Control	G1: Certified medical assistant made calls at 3, 7, 14, 21, and 28 days following clinic visit; subjects asked whether any problems were experience with medication; adverse events were discussed and solutions offered to minimize toxicities; when adverse events severe or could not be properly evaluated or prescription drug necessary to control adverse event, additional telephone contact arranged with physician or clinical pharmacist G2: No telephone contact	Niacin or bile acid sequestrants (BAS)
Schneider et al., 2008[49] N-A	G1: Study group G2: Control group	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	Lisinopril
Schnipper et al., 2006[50] NA	G1: Pharmacist intervention G2: Usual care	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 non-adherence), and reviewed the medication directions with the patient. During a follow-up phone call at 5 days post-discharge, 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.	Medications for multiple conditions
Simon et al., 2006[51] na	G1: Telephone care management G2: UC	G1: 3 phone contacts - each contact included a brief, structured assessment of current depressive symptoms, current use of AD medication, and AD side effects. During phone contacts, care managers followed specific scripts to address concerns regarding side effects and used scripted motivational enhancement techniques to address common reasons for discontinuing medication. The treating psychiatrist received a structured report of each contact, including a summary of the clinical assessment and algorithm based recommendations regarding antidepressant medication adjustment. If a change in treatment was recommended, the care manager contacted the psychiatrist to facilitate doctor-patient communication and follow-up. Care managers also provided as-needed crisis intervention and care coordination. G2: All participants were contacted for blinded telephone outcome assessments three and six months after being randomly assigned to the study groups.	Depression medications
Sledge et al., 2006[52] N-A	G1: Primary Intensive Care G2: Usual care	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.	Medications for multiple conditions

Table D1. Description of intervention and comparison groups (continued)

Author, Year Trial name	Groups	Interventions and Comparators	Medication Name(s)/ Class(es)/Indication(s)
Smith et al., 2008[53] NR	G1: Mailed communications to patients and primary care providers G2: Usual care	G1: Patients received 2 mailed communications approximately 2 months apart stressing the importance of lifetime use of beta blockers following MI and also that adverse effects can be managed and the importance of remembering to refill their prescription. They also included a brief mention of other therapies (statins, ACEIs, and aspirin). Both mailings included a wallet card with suggested questions to ask their clinician, space to list their medications, and space to record additional queries. Primary care clinicians of patients randomized to the intervention arm received sample materials and a letter alerting them that their patients with MI would be receiving materials developed with input from patients and clinicians in primary care and cardiology. The letters asked the primary care clinicians to support the initiative and reminded them of guidelines on lifetime use of beta blockers following MI. G2: Neither patients or clinicians in this group contacted	Beta blockers
Solomon et al., 1998[54] NA Gourley et al., 1998[55] NA	G1: Pharmaceutical care (HTN and COPD subgroups) G2: Traditional pharmacy care (HTN and COPD subgroups)	G1: Pharmaceutical care intervention group underwent a six month treatment period with scheduled visits at enrollment and then at 4-6 week intervals to total 5 visits with an assigned pharmacist; the intervention also consisted of standardized patient assessment activities and a series of regularly scheduled therapeutic and educational interventions designed for optimal disease management. G2: The traditional pharmacy care control group had only two visits, one at baseline and one at 6 months; they did not have access to the primary pharmacy caregivers and received no supplemental education or assessment of needs beyond what was customarily offered at each site. Traditional pharmacy care ranged from non-standardized interventions to distribution of product only.	Dihydropyridine or dihydropyridine and diuretic therapy for hypertensives; At least 1 metered dose inhaler for the treatment of COPD for those with COPD.
Stacy et al., 2009[56] NA	G1: Experimental G2: Enhanced Care Control	G1: Received up to 3 separate tailored behavioral support interventions delivered via an interactive voice recognition (IVR) system coupled with tailored print material receive through the mail. Calls provided highly tailored messages that specifically reinforced adherence/persistence with statins using a combination of behavioral science theories and techniques. Subsequent calls referred to health plan website for info. on dyslipidemia, risk reduction, and lipid lowering drugs. Mail provided tailored messages to enhance commitment, improve communication w/ health care team, and address adherence barriers. G2: Received non-tailored behavioral advice from a single IVR call at baseline, coupled with an untailored, generic, self-help cholesterol management guide received through the mail. Guide provided educational material on cholesterol and lipid values, a brief knowledge quiz, and an untailored action plan but did not address medication adherence.	Statin

Table D1. Description of intervention and comparison groups (continued)

Author, Year Trial name	Groups	Interventions and Comparators	Medication Name(s)/ Class(es)/Indication(s)
Taylor et al., 2003[57] NA	G1: Pharmaceutical care G2: Standard care	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.	Medications for multiple conditions (unspecified)
Vivian et al., 2002[58] NA	G1: Clinical pharmacist intervention G2: Control	G1: Patients saw clinical pharmacist once/month at a pharmacist-managed hypertension clinic; pharmacist had prescribing authority and made appropriate therapy changes for BP in accordance to JNC VI guidelines; did not make any changes to other drugs that may adversely affect BP; drug counseling (on side effects, recommend lifestyle changes, and assessment of compliance) provided at each visit; allowed to receive care for comorbid conditions from PCPs but could not make changes to antihypertensive drug regimens G2: Received traditional pharmacy services (dispensing, brief counseling about drugs, review of drug profiles); no monthly visits to pharmacist-managed hypertension clinic; received care from PCPs as needed at least once a year	Antihypertensive medications
Waalen et al., 2009[59] NA	G1: "Virtual" osteoporosis clinic G2: Usual care	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, and then monthly calls until the patient started taking the medication and reported no problems. They were given a 3-month prescription for a second-generation bisphosphonate. 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 follow-up. 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.	Osteoporosis medication

Table D1. Description of intervention and comparison groups (continued)

Author, Year Trial name	Groups	Interventions and Comparators	Medication Name(s)/ Class(es)/Indication(s)
Wakefield et al., 2011[60] NA	G1: High intensity nurse- managed home telehealth intervention G2: Low intensity nurse- managed home telehealth intervention G3: Usual care	G1: using the home telehealth device, pts entered BP and BG and responded to standardized questions. Pts then received appropriate automated responses depending on how they answered the device prompt. Pt data downloaded and made available for the nurse to review who determined whether the subject needed additional health information, increased monitoring, compliance strategies, problem resolution facilitation, or contact with the subject's physician. Study team developed algorithm based guidelines programmed into device. Schedule established for each prompt set so that subjects received both standard prompts each day and a rotation of questions and educational content. G2: Same as G1 excpet responded to a smaller subset of questions; did not use branching algorithm, rather used yes/no or multiple choice responses. G3: scheduled follow-up appointments w/ the primary care clinic in usual manner; had access to their nurse care manager	NR
Weinberger et al., 2002[61] NA	G1: Pharmaceutical Care Program G2: Peak Flow Monitoring Control Group G3: Usual Care Control Group	G1: Broadly included Pharmacist training (interpretation of patient-specific data, technique to measure peak flow, instructions on counseling), availability of patient specific data via computer (patient background, contact info, peak flow rates, ED/hospital visits, medication/med possession ratio), written patient education materials for handouts to patients, resource guide for pharmacists, and implementation of "pragmatic strategies" to encourage pharmacists to implement program. G2: Pharmacist training in reactive airway disease, diabetes, HTN; patient given peak flow meter, trained on its use, and monthly calls to elicit peak flows; data not provided to pharmacists G3: Same pharmacist training in G2, patient not given peak flow meter	Meds for reactive airway disease (i.e. COPD or asthma)
Weymiller et al., 2007[62] Statin Choice Randomized Trial Jones et al., 2009[63] Statin Choice Randomized Trial	G1: Decision Aid G2: Control G1 (Statin Choice before visit): 26 G2 (Statin Choice during visit): 26 G3 (Control before visit): 23 G4: (Control during visit): 23	G1: The one-page *Statin Choice* decision aid which included the patient's name, cardiovascular risk factors, and 1 of 3 levels of baseline 10-year cardiovascular risk (risk levels specified in article). It also showed the absolute risk reduction associated with taking statins and the potential disadvantages. Patients were prompted to express their readiness to take statins, discuss the issues with their primary care clinician or another important person, or delay the decision until another time. In addition, a multiple-page pamphlet was included that provided detail with visual links to the tailored one-page version, facilitating patient review of the material after the visit. G2: A Mayo Clinic standard educational pamphlet which defined lipid disorders and provided dietary guidelines for control of cholesterol, along with general statements encouraging exercise and smoking cessation.	Statins

Table D1. Description of intervention and comparison groups (continued)

Author, Year Trial name	Groups	Interventions and Comparators	Medication Name(s)/ Class(es)/Indication(s)
Williams et al., 2010[64] NA	G1: Patients in practices where MDs were instructed how to access and interpret electronic adherence data G2: Patients in usual care, included education	G1: Physicians receive electronic adherence data and specific instructions on how to interpret that data G2: Both groups received an audio compact disc, digital video disc, and booklet (all had same content) on the most recent national asthma guidelines and methods for discussing medication nonadherence with their patients; material emphasized a non-confrontational approach to discussing adherence and included ways to identify barriers to taking medication, tips to help patients remember to take their medication, and methods to promote patient self-efficacy.	ICS
Wilson et al., 2010[65] Better Outcomes of Asthma Treatment (BOAT); note that there is online supplemental material for methods and timeline	G1: Shared decision making G2: Clinical decision making G3: Usual care	G1: SDM: At study visits, care managers provide information and share decision-making responsibility with patients; treatment decisions negotiated by incorporating patient preferences and goals. Barriers to adherence addressed using motivational techniques. Progress was assessed at subsequent study visits and in three brief phone calls; medications adjusted as necessary. For care managers who are not licensed to prescribe, physicians reviewed and wrote prescriptions. Study care managers document each patient encounter in medical charts where it is available to patient's physician. G2: CDM – Identical to SDM in process except study care managers only recommend new treatment regimens based on guidelines, without identifying patient goals/preferences or negotiating treatments/decisions. G3: Usual Care: stepped care approach to medications with the aim of long-term asthma control.	Asthma medications
Wolever et al., 2010[66] NA	G1: 6 months integrative health coaching G2: Usual care	G1: 6 months of integrative health coaching, a personalized intervention that assists people in identifying their own values and vision of health, followed by a follow-up visit G2: Those randomized to the control group received no materials or correspondence during the 6-month period	Oral diabetes medication
Zhang et al., 2010[67] NA	G1: Medicare Part D prescription drug coverage G2: Medicare Part D prescription drug coverage G3: Medicare Part D prescription drug coverage G4: Remained on retiree health benefit coverage	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, which was covered by retiree health benefits had no deductible, paid copayments of $10 - $20 per monthly prescription	Hyperlipidemia, diabetes, and hypertension medications

Table D2. Study characteristics, part 1

Author, Year Trial Name	N Eligible	N Randomized	N Completers	N Analyzed	Study Design
Bender et al., 2010[1] NA	NR	Overall N: 50 G1: 25 G2: 25	NR	Overall N: 50 G1: 25 G2: 25	RCT: parallel, not clustered
Berg et al., 1997[2] NA	Overall N: 87 G1: NR G2: NR	Overall N: 55 G1: 31 G2: 24	Overall N: 54 G1: NR G2: NR	Overall N: 55 G1: 31 G2: 24	Non-clustered RTC with block randomization by asthma severity
Berger et al., 2005[3] NA	Overall N: NR G1: G2:	Overall N: 435 G1: 212 G2: 212 (the article does not account for the discrepancy in these numbers)	Overall N: 367 G1: 172 G2: 195	Overall N: 367 G1: 172 G2: 195	RCT: parallel, not clustered
Bogner et al., 2008[4] NA	Overall N: 109 prescreened as potentially eligible - 73 provided consent for screening G1: NR G2: NR	Overall N: 64 G1: 32 G2: 32	Overall N: 64 G1: 32 G2: 32	Overall N: 64 G1: 32 G2: 32	RCT: parallel, not clustered
Bogner et al., 2010[5] NA	Overall N: 58 G1: 29 G2: 29	Overall N: 58 G1: 29 G2: 29	Overall N: 58 G1: 29 G2: 29	Overall N: 58 G1: 29 G2: 29	RCT: parallel, not clustered
Bosworth et al., 2005[6] V-STITCH	Overall N: 816 G1: NR G2: NR	Overall N: 588 G1: 294 G2: 294	Overall N: NR G1: NR G2: NR	Overall N: NR G1: NR G2: NR	RCT: parallel, not clustered
Bosworth et al., 2008[7] TCYB Bosworth et al., 2007[8] TCYB Methods paper	Overall N: NR, unclear from text G1: NR G2: NR	Overall N: 636 G1: 319 G2: 317	Overall N: NR G1: NR G2: NR	Overall N: NR G1: NR G2: NR	RCT: parallel, not clustered
Capoccia et al., 2004[9] NA	Overall N: 89 G1: G2:	Overall N: 74 G1: 41 G2: 33	Overall N: 69 G1: 37 G2: 30	Overall N: 74 G1: 41 G2: 33	RCT: parallel, not clustered

Author, Year Trial Name	N Eligible	N Randomized	N Completers	N Analyzed	Study Design
Carter et al., 2009[10] NA	Overall N: 1242 G1: 568 G2: 674	Overall N: 402 G1: 192 G2: 210	Overall N: 332 G1: 158 G2: 174	Overall N: 402 G1: 192 G2: 210	RCT: cluster-randomized
Chernew et al., 2008[11] NA	Number of members in health plan Overall N (2004): G1: 35,807 G2: 74,345 Overall N (2005): G1: 37,867 G2: 70,259	NA	NR	For diabetes medications: 2004 (Pre): G1: 919 to 1,245 G2: 3,596 to 4,185 2005 (Post): G1:1,056 to 1,306 G2: 3,535 to 4,072 Unit of observation in analyses was patient-quarter, yielding eight observations per patient	Before-after study
Choudhry et al., 2010[12] NA	Overall N: 52,631 G1: 2051 G2: 779 G3: 38,174 G4: 11,627	Overall N: NA G1: NA G2: NA	Overall N: 52,631 G1: 2051 G2: 779 G3: 38,174 G4: 11,627	Overall N: 52,631 G1: 2051 G2: 779 G3: 38,174 G4: 11,627	Other
Choudhry et al., 2011[13] MI FREEE	Overall N: 6768 G1: G2:	Overall N: 5855 G1: 2845 G2: 3010	Overall N: 5571 G1: 2712 G2: 2859	Overall N: 5571 G1: 2712 G2: 2859	RCT: cluster-randomized
Friedman et al., 1996[14] NA	Overall N: 964 G1: NR G2: NR	Overall N: 299 G1: NR G2: NR	Overall N: 267 G1: 133 G2: 134	Overall N: 267 G1: 133 G2: 134	RCT: parallel, not clustered
Fulmer et al., 1999[15] NA	Overall N: 600 G1: G2:	Overall N: 60 G1: NR G2: NR G3: NR	Overall N: 50 G1: 17 G2: 15 G3: 18	Overall N: 50 G1: 17 G2: 15 G3: 18	RCT: parallel, not clustered
Grant et al., 2003[16] NA	Overall N: 462 G1: 118 G2: 114 G3: 230	Overall N: 462 G1: 118 G2: 114 G3: 230	Overall N: 120 G1: 62 G2: 58	Overall N: 120 G1: 62 G2: 58	RCT: parallel, not clustered

Author, Year Trial Name	N Eligible	N Randomized	N Completers	N Analyzed	Study Design
Guthrie et al., 2001[17] First Myocardial Infarction (MI) Risk Reduction Program	Overall N: NR G1: NR G2: NR	Overall N: 13,100 G1: 10,335 G2: 2,765	Overall N: 4548 G1: 3635 G2: 913	Overall N: 4548 G1: 3635 G2: 913	RCT: parallel, not clustered
Hoffman et al., 2003[18] NA	NR	Overall : Patients: 9564 Providers: 7021 G1: Patients: 4899 Providers: 3474 G2: Patients: 4665 Providers: 3547	Overall N: G1: G2:	Overall N: G1: G2:	RCT: cluster-randomized
Hunt et al., 2008[19] NA	Overall N: 2,901 G1: NR G2: NR	Overall N: 463 G1: 230 G2: 233	Overall N: 272 G1: 142 G2: 130	Overall N: 272 G1: 142 G2: 130	RCT: parallel, not clustered
Janson et al., 2003[20] NA	Overall N: NR G1: NR G2: NR	Overall N: 68 G1: NR G2: NR	Overall N: 62 G1: NR G2: NR	Overall N: 65 G1: 33 G2: 32	RCT: parallel, not clustered
Janson et al., 2009[21] NA	Overall N: 95 G1: NA G2: NA	Overall N: 84 G1: 45 G2: 39	NR	Overall N: G1: 45 G2: 39	RCT: parallel, not clustered
Johnson et al., 2006[23] NR	Overall N: 1227 G1: NR G2: NR	Overall N: NR G1: NR G2: NR	Overall N: NR G1: NR G2: NR	Overall N: 1017 G1: 500 G2: 517	RCT: parallel, not clustered
Johnson et al., 2006[22] NR	Overall N: 1038 G1: NR G2: NR	Overall N: 404 G1: 202 G2: 202	Overall N: 262 G1: 114 G2: 148	Overall N: 404 G1: 202 G2: 202	RCT: parallel, not clustered
Katon et al., 1995[24] NA	Overall N: 242 G1: G2:	Overall N: 217 Major depression group N: 91 G1: 49 G2: 42 Minor depression group N: 126 G1: 59 G2: 67	Overall N: 177 G1: NR G2: NR	Overall N: 177 G1: NR G2: NR	RCT: cluster-randomized

Author, Year Trial Name	N Eligible	N Randomized	N Completers	N Analyzed	Study Design
Katon et al., 1996[25] NA	Overall N: 183	Overall N: 153 G1: 77 G2: 76 Major depression: 65 Minor depression: 88	Overall N: 113 G1: 60 G2: 53	N analyzed NR, but stated to include "all intervention patients" for adherence outcomes, unclear for other outcomes	RCT: cluster-randomized
Katon et al., 2001[28] NA Ludman et al., 2003[29] NA Van Korff et al., 2003[30] NA	Overall N: 480	Overall N: 386 G1: 194 G2: 192	Overall N: 315 G1: 170 G2: 145	Overall N: 315 G1: 170 G2: 145	RCT: parallel, not clustered
Katon et al., 1999[26] NA Katon et al., 2002[27] NA	Overall N: 341	Overall N: 228 G1: 114 G2: 114	6 m:Overall N: 167 G1: 87 G2: 80 28 m: Overall N: 171 G1: NR G2: NR	6 m:Overall N: 228 G1: 114 G2: 114 28 m:Overall N: 187 G1: 95 G2: 92	RCT: parallel, not clustered
Lee et al., 2006[31] FAME	Overall N: 208 G1: NR G2: NR	Overall N: 159 G1: 83 G2: 76	Overall N: 146 G1: 77 G2: 69	Overall N: 159 G1: 83 G2: 76	RCT: parallel, not clustered
Lin et al., 2006[32] NA	Overall N: 375 G1: NA G2: NA	Overall N: 329 G1: 164 G2: 165	Overall N: NR	Overall N: 329 G1: 164 G2: 165	RCT: parallel, not clustered

Author, Year Trial Name	N Eligible	N Randomized	N Completers	N Analyzed	Study Design
Maciejewski et al., 2010[3315257] NA	Overall N: NR G1: NR G2: NR	Enrollees Overall N: 1385391 G1: 747300 G2: 638091 All employers Overall N: 32259 G1: 32083 G2: 176 Underwritten employers Overall N: 32032 G1: 32032 G2: 0 Self-insured employers Overall N: 227 G1: 51 G2: 176	Overall N: NR G1: NR G2: NR	Enrollees **Overall N**: 1385391 G1: 747300 G2: 638091 **Diuretics** Overall N: NR G1: 15605 G2: 9137 **ACE Inhibitors** Overall N: NR G1: 14250 G2: 7668 **Statins** Overall N: NR G1: 18346 G2: 10162 **Beta Blockers** Overall N: NR G1: 11137 G2: 6343 **Calcium Channel Blockers** Overall N: NR G1: 7191 G2: 4099 **Metformin** Overall N: NR G1: 5077 G2: 2826 **ARBs** Overall N: NR G1: 7445 G2: 4514 **Cholesterol Absorption Inhibitors** Overall N: NR G1: 4019 G2: 2291	Retrospective quasi-experimental
Mann et al., 2010[34] The Statin Choice	NR	Overall N: 150 G1: 80 G2: 70	NR	NR	RCT: parallel, not clustered

Author, Year Trial Name	N Eligible	N Randomized	N Completers	N Analyzed	Study Design
Montori et al., 2011[35] NA	Overall N: 102 G1: NA G2: NA	Overall N: 100 G1: 52 G2: 48	Overall N: 93 G1: 47 G2: 46	Overall N: 100 G1: 52 G2: 48	RCT: parallel, not clustered
Murray et al., 2007[36] NA	Overall N: 1512 G1: NR G2: NR	Overall N: 314 G1: 122 G2: 192	Overall N: 270 G1: 106 G2: 164	Overall N: 314 G1: 122 G2: 192	Randomized clinical trial
Nietert et al., 2009[37] NA	Overall N: 3048 G1: NR G2: NR G3: NR	Overall N: 3048 G1: 1018 G2: 1016 G3: 1014	Overall N: 2590 G1: 869 G2: 863 G3: 858	Overall N: 3048 G1: 1018 G2: 1016 G3: 1014	RCT: parallel, not clustered
Okeke et al., 2009[38] NA	Overall N: 66 G1: G2:	Overall N: 66 G1: 35 G2: 31	Overall N: NR G1: NR G2: NR	Overall N: 66 G1: 35 G2: 31 *4 excluded from multivariate analysis (1 from G1 and 2 from G2) due to missing value in education (N=2), Asian race (N=1), and use of travoprost without using dosing aid (N=1)	RCT: parallel, not clustered
Pearce et al., 2008[39] Cardiovascular Risk Education and Social Support (CaRESS) Trial	Overall N: 233 G1: NR G2: NR G3: NR	Overall N: 199 G1: 50 G2: 58 G3: 91	Overall N: 153 G1 + G2: 81 G3: 72	Overall N: 199 G1: 50 G2: 58 G3: 91	RCT: cluster-randomized
Powell et al., 1995[40] NA	Overall N: NR G1: NR G2: NR	Overall N: 4246 G1: 1993 G2: 2253	Overall N: 4246 G1: 1993 G2: 2253	Overall N: 4246 G1: 1993 G2: 2253	RCT: cluster-randomized
Powers et al., 2011[68]	Overall N: 278 G1: NR G2: NR	Overall N: 89 G1: 44 G2: 45	Overall N: 89 G1: 44 G2: 45	Overall N: 89 G1: 44 G2: 45	RCT: parallel, not clustered
Pyne et al., 2011[41] HIV Translating Initiatives for Depression Into Effective Solutions (HITIDES)	Overall N: 448 G1: NA G2: NA	Overall N: 276 G1: 138 G2: 138	Overall N: 225 G1: 105 G2: 110	Overall N: 249 G1: 123 G2: 126	RCT: parallel, not clustered

Author, Year Trial Name	N Eligible	N Randomized	N Completers	N Analyzed	Study Design
Rich et al., 1996[42] NA	Overall N: NR G1: NR G2: NR	Overall N: 156 G1:80 G2: 76	Overall N: NR G1: NR G2: NR	Overall N: 156 G1:80 G2: 76	RCT: parallel, not clustered
Rickles et al., 2005[43] NA	Overall N: 63 G1: G2:	Overall N: 63 G1: 31 G2: 32	Overall N: G1: 28 G2:32	Overall N: G1: 28 G2: 32	RCT: parallel, not clustered
Ross et al., 2004[44] NR	Overall N: NR G1: NR G2: NR	Overall N: 107 G1: 54 G2: 53	Overall N: 81 G1: 38 G2: 43	Overall N: NR G1: NR G2: NR	RCT: parallel, not clustered
Rudd et al., 2004[45] NA	Overall N: 837 G1: NR G2: NR	Overall N: 150 G1: 74 G2: 76	Overall N: 137 G1: 69 G2: 68	Overall N: 150 G1: 74 G2: 76	RCT: parallel, not clustered
Rudd et al., 2009[46] NA	Overall N: 408 G1: G2:	Overall N: 127 G1: 64 (51 Individualized Care, 13 Plain English) G2: 63	Overall N: 105 G1: 48 G2: 57	Overall N: 127 G1: 64 G2: 63	Other
Schaffer et al., 2004[47] NA	Overall N: NR G1: NR G2: NR G3: NR G4:NR	Overall N: 46 G1: NR G2: NR G3: NR G4:NR	Overall N: 44 G1: NR G2: NR	Overall N: 46 G1: 11 G2: 10 G3:12 G4:13	RCT: parallel, not clustered
Schectman et al., 1994[48] NA	Overall N: NR Niacin G1: 102 BAS G2: 62	Niacin Overall N: 102 G1: 52 G2: 50 BAS Overall N: 62 G1: 31 G2: 31	Niacin Overall N: 102 G1: 52 G2: 50 BAS Overall N: 60 G1: 29 G2: 31	Niacin Overall N: 80 G1: 40 G2: 40 BAS Overall N: 40 G1: 18 G2: 22	RCT: parallel, not clustered
Schneider et al., 2008[49] NA	Overall N: 112 G1: NR G2: NR	Overall N: 93 G1: NR G2: NR	Overall N: 85 G1: 47 G2: 38	Overall N: 85 G1: 47 G2: 38	RCT: parallel, not clustered
Schnipper et al., 2006[50] NA	Overall N: 291 G1: G2:	Overall N: 178 G1: 92 G2: 84	Overall N: 152 G1: 79 G2: 73	Overall N: 152 G1: 79 G2: 73	RCT: parallel, not clustered

Author, Year Trial Name	N Eligible	N Randomized	N Completers	N Analyzed	Study Design
Simon et al., 2006[51] NA	Overall N: 217 G1: NR G2: NR	Overall N: 207 G1: NR G2: NR	Overall N: NR G1: NR G2: NR	Overall N: G1: symptom analysis: 94 utilization analysis: 98 G2: symptom analysis: 94 utilization analysis: 97	RCT: parallel, not clustered
Sledge et al., 2006[52] NA	Overall N: 238 G1: G2:	Overall N: 96 G1: 47 G2: 49	Overall N: 75 G1: 36 G2: 39	Overall N: 75 G1: 36 G2: 39	RCT: parallel, not clustered
Smith et al., 2008[53] NR	Overall N: NR G1: NR G2: NR	Overall N: 907 G1: 458 G2: 449	Overall N: 836 G1: 426 G2: 410	Overall N: 836 G1: 426 G2: 410	RCT: cluster-randomized
Solomon et al., 1998[54] NA Gourley et al., 1998[55] NA	Overall N: NR G1: NR G2: NR	Overall N: NR G1: NR G2: NR	Overall N: HTN:133 COPD:98 G1 (HTN): 63 G2 (HTN): 70 G1 (COPD): 43 G2 (COPD): 55	Overall N: HTN: 133 COPD: 98 G1 (HTN): 63 G2 (HTN):70 G1 (COPD): 43 G2 (COPD): 55	RCT: parallel, not clustered
Stacy et al., 2009[56] NA	Overall N: 5174 G1: G2:	Overall N: 578 G1: 298 G2: 280	Overall N: 497 G1: 253 G2: 244	Overall N: 497 G1: 253 G2: 244	RCT: parallel, not clustered
Taylor et al., 2003[57] NA	Overall N: NR G1: G2:	Overall N: 81 G1: NR G2: NR	Overall N: 69 G1: 33 G2: 36	Overall N: 69 G1: 33 G2: 36	RCT: parallel, not clustered
Vivian et al., 2002[58] NA	Overall N: 56 G1: NA G2: NA	Overall N: 56 G1: 27 G2: 29	Overall N: 53 G1: 26 G2: 27	Overall N: 53 G1: 26 G2: 27	RCT: parallel, not clustered
Waalen et al., 2009[59] NA	Overall N: 442 G1: G2:	Overall N: 235 G1: 125 G2: 110	Overall N: 211 G1: 109 G2: 102	Overall N: 211 G1: 109 G2: 102	RCT: parallel, not clustered
Wakefield et al., 2011[60]	Overall N: 304 G1: NR G2: NR G3:NR	Overall N: 302 G1: 93 G2: 102 G3: 107	Overall N: 246 G1: 73 G2: 79 G3: 94	Overall N: NR G1: NR G2: NR G3:NR	RCT: parallel, not clustered

Author, Year Trial Name	N Eligible	N Randomized	N Completers	N Analyzed	Study Design
Weinberger et al., 2002[61] NA	Overall N: 14195 G1: NR G2: NR G3:N Religible for initial criteria	Overall N: 1113 G1: 446 G2: 363 G3: 303	Overall N: 898 G1: 356 G2: 296 G3: 246	Overall N: 898 G1: 356 G2: 296 G3: 246	RCT: cluster-randomized
Weymiller et al., 2007[62] Statin Choice Randomized Trial Jones et al., 2009[63] Statin Choice Randomized Trial	Overall N: 124 G1: NA G2: NA	Overall N: 98 G1: 52 G2: 46	Overall N: 97 G1: 51 G2: 46	Overall N: 97 G1: 51 G2: 46	RCT: cluster-randomized
Williams et al., 2010[64] NA	Overall N: 207 MDs (34 practices) G1: NA G2: NA	Overall N: 34 practices (207 providers); G1: 17 practices (88 providers; 1335 patients) G2: 17 practices (105 providers; 1363 patients)	Overall N: 34 practices (206 providers) G1: 17 practices (87 providers; 1040 patients); G2: 17 practices (105 providers; 1034 patients)	Overall N: G1: G2:	RCT: cluster-randomized
Wilson et al., 2010[65] Better Outcomes of Asthma Treatment (BOAT)	Overall N: 1070 G1: G2:	Overall N: 612 G1: 204 G2: 204 G3: 204	Overall N: 551 G1: 182 G2: 180 G3: 189	Varies by outcome	RCT: parallel, not clustered
Wolever et al., 2010[66] NA	Overall N: 64 G1: NR G2: NR	Overall N: 56 G1: 30 G2: 26	Overall N: 47 G1: 25 G2: 22	Overall N: 49 G1: 27 G2: 22	RCT: parallel, not clustered
Zhang et al., 2010[67] NA	Overall N: 20,889 G1,G2,G3: Total of 14,965 G4: 5,924	NA	NA	Overall N: 20,889 G1, G2, G3: Total of 14,965 G4: 5924	Before-after study

Table D3. Study characteristics, part 2

Author, Year Trial Name	Level of Randomization	Setting: Geography	Healthcare Setting	Study Duration (Months)	Funding Source
Bender et al., 2010[1] NA	Patient	National Jewish Health in Denver, CO	tertiary care center	2.3	Pharma
Berg et al., 1997[2] NA	Patient	NR; rural	community	1.61	Glaxo and NINR (gov't - national institute of nursing)
Berger et al., 2005[3] NA	Patient	US	network of patients with MS contacted by Biogen	3	Pharma
Bogner et al., 2008[4] NA	Patient	West Philadelphia with 12 family physicians	community-based primary care practice	1.38	Multiple
Bogner et al., 2010[5] NA	Patient	Philadelphia	Community-based primary care clinic	2.76	Multiple
Bosworth et al., 2005[6] V-STITCH	Patient	Durham, NC	outpatient VA primary care clinic	24 months for entire study, this paper reports 6 month outcomes	Gov't
Bosworth et al., 2008[7] TCYB Bosworth et al., 2007[8] TCYB Methods paper	Patient	North Carolina	primary care clinic	24 months planned, this paper reported 6 month outcomes	Multiple
Capoccia et al., 2004[9] NA	Patient	The University of Washington Family Medical Center (UWFMC)	primary care clinic in	12	Foundation or non-profit
Carter et al., 2009[10] NA	Practice (e.g., clinic, residential care facility)	Iowa: Davenport, Des Moines, Mason City, Sioux City, & Waterloo	6 community-based family medicine residency programs	6	Gov't
Chernew et al., 2008[11] NA	Other	NR	Administrative data	24	Pharma
Choudhry et al., 2010[12] NA	Other	NR.	Intervention implemented by a pharmacy benefits management company	24	Foundation or non-profit

Author, Year Trial Name	Level of Randomization	Setting: Geography	Healthcare Setting	Study Duration (Months)	Funding Source
Choudhry et al., 2011[13] MI FREEE	Randomized at level of insurance plan	USA--members of Aetna insurance plan	Insurance Plan	Median duration of follow up = 13.1 months	Multiple
Friedman et al., 1996[14] NA	Patient	Boston, MA	Screening occurred at community sites such as senior centers; intervention and baseline and 6-month assessments occurred at patients' homes	6	Gov't
Fulmer et al., 1999[15] NA	Patient	Manhattan in New York City, NY	Recruitment from large urban home health care agency and a large urban ambulatory care clinic; interventions delivered via phone and data collection in participants' homes	2.3	Multiple
Grant et al., 2003[16] NA	Patient	a predominantly working class community approximately 10 miles north of Boston	academically-affiliated community health center	3	Multiple
Guthrie et al., 2001[17] First Myocardial Infarction (MI) Risk Reduction Program	Patient	NR	primary care clinic	6	Pharma
Hoffman et al., 2003[18] NA	Other	Florida, IPA-model HMO	Pharmacies	6	Multiple
Hunt et al., 2008[19] NA	Patient	Oregon	Primary care	12	Pharma
Janson et al., 2003[20] NA	patient	NR	clinical laboratory	1.61	Gov't
Janson et al., 2009[21] NA	Patient	San Francisco Bay Area	Recruited from private and public community clinics in the San Francisco Bay Area - setting of face-to-face settings not described	5.52 (included 4-week run-in period; 4-week intervention period, and 14 weeks of observation)	Other

Author, Year Trial Name	Level of Randomization	Setting: Geography	Healthcare Setting	Study Duration (Months)	Funding Source
Johnson et al., 2006[23] NR	Patient	New England	HMO recruitment; Mail-based intervention	18	Gov't
Johnson et al., 2006[22] NR	Patient	Rhode Island	NR	18	Gov't
Katon et al., 1995[24] NA	patient	Washington State	primary care clinic	7	Gov't
Katon et al., 1996[25] NA	Patient	Seattle, WA	large primary care clinic	7	Gov't
Katon et al., 2001[28] NA Ludman et al., 2003[29] NA Van Korff et al., 2003[30] NA	Patient	Washington State	4 large primary care clinics in a group-model HMO	12	Gov't
Katon et al., 1999[26] NA Katon et al., 2002[27] NA	Patient	large group-model HMO in Washington State	primary clinics	28	Gov't
Lee et al., 2006[31] FAME	Patient	Washington DC	university-affiliated, tertiary care US military medical center	14 -Run-in x 2 months - Phase 1 observational months 3-8 - RCT months 9-14	Professional organization
Lin et al., 2006[32] NA	Patient	State of Washington	9 primary care clinics of Group Health Cooperative (GHC)	12	Gov't
Maciejewski et al., 2010[3315257] NA	NA	Several states, mostly North Carolina (NC)	N/A	24	Foundation, Gov't, Other (Insurer)

Author, Year Trial Name	Level of Randomization	Setting: Geography	Healthcare Setting	Study Duration (Months)	Funding Source
Mann et al., 2010[34] The Statin Choice	Patient	NR	urban primary care practice serving primarily minority population	6	Unspecified
Montori et al., 2011[35] NA	Patient	Rochester, MN	General medicine and primary care practices	6	Foundation or non-profit
Murray et al., 2007[36] NA	Patient	Indianapolis, Indiana	Pharmacies	12	Gov't
Nietert et al., 2009[37] NA	Patient	South Carolina	9 pharmacies within a medium-sized grocery store chain	Unclear	Gov't
Okeke et al., 2009[38] NA	Patient	Pennsylvania, PA and Baltimore, MD	Two eye clinics	Observational cohort: 3 RCT: 3	Multiple
Pearce et al., 2008[39] Cardiovascular Risk Education and Social Support (CaRESS) Trial	Practice (e.g., clinic, residential care facility)	Kentucky	18 primary care practices in the Kentucky Ambulatory Network practice-based research network	2.76 in first 15 practice sites, 2.07 in last 3 sites	Gov't
Powell et al., 1995[40] NA	Patient	Midwestern United States	Homes	9	Multiple
Powers et al., 2011[68]	Patient	Durham, NC	primary care clinic	3	Gov't
Pyne et al., 2011[41] HIV Translating Initiatives for Depression Into Effective Solutions (HITIDES)	Patient	Little Rock, Arkansas	VA HIV clinics	12	Gov't
Rich et al., 1996[42] NA	Patient	NR	university teaching hospital	1	Gov't
Rickles et al., 2005[43] NA	Patient	Wisconsin	recruitment from pharmacies	6	Gov't

Author, Year Trial Name	Level of Randomization	Setting: Geography	Healthcare Setting	Study Duration (Months)	Funding Source
Ross et al., 2004[44] NR	Patient	Denver, CO	specialty clinic for heart failure	12	Foundation or non-profit
Rudd et al., 2004[45] NA	Patient	California	primary care clinic	6	Other
Rudd et al., 2009[46] NA	Patient	NR	Arthritis center in urban teaching hospital	12	Gov't
Schaffer et al., 2004[47] NA	Patient	not specifically reported; possibly Florida	NR	6	Academic
Schectman et al., 1994[48] NA	Patient	Milwaukee, WI	VA medical center	6;, only 2-month results reported	Multiple
Schneider et al., 2008[49] NA	Patient	Columbus, OH and Tucson, AZ	Ambulatory care clinics	12	Gov't
Schnipper et al., 2006[50] NA	patient	Boston, MA	Hospital	1	Multiple
Simon et al., 2006[51] NA	Patient	Washington and Northern Idaho	members of Group Health cooperative - contacted if prescribed psychological medication from a psychiatrist	6	Multiple
Sledge et al., 2006[52] NA	Patient	Northeastern US	Primary care center of an urban, academically affiliated hospital	12	Multiple
Smith et al., 2008[53] NR	Practice (e.g., clinic, residential care facility)	Boston, MA Atlanta, GA Portland, OR Minneapolis, MN	primary care clinic	2	Gov't
Solomon et al., 1998[54] NA Gourley et al., 1998[55] NA	Patient	10 Veterans Affairs Medical Centers and 1 University hospital	Pharmacies	6	Pharma

Author, Year Trial Name	Level of Randomization	Setting: Geography	Healthcare Setting	Study Duration (Months)	Funding Source
Stacy et al., 2009[56] NA	Patient	NR	managed care HMO or PPO members	6	Other
Taylor et al., 2003[57] NA	patient	Aliceville, AL and Gordo, AL	Community-based physician offices	12	Unspecified
Vivian et al., 2002[58] NA	Patient	Philadelphia	Pharmacy-based at VAMC	6	Foundation or non-profit
Waalen et al., 2009[59] NA	Patient	San Diego, CA	Kaiser Permanente Department of Preventive Medicine	12	Pharma
Wakefield et al., 2011[60]	Patient	Iowa City, Iowa	VA primary care clinic	12	Gov't
Weinberger et al., 2002[61] NA	Pharmacy	Indianapolis, IN	pharmacy	12	Gov't
Weymiller et al., 2007[62] Statin Choice Randomized Trial Jones et al., 2009[63] Statin Choice Randomized Trial	Other	Minnesota	Metabolic clinic at the Mayo Clinic	3	Multiple
Williams et al., 2010[64] NA	Practice (e.g., clinic, residential care facility)	Southeast Michigan including Detroit	primary care clinics	12	Gov't
Wilson et al., 2010[65] Better Outcomes of Asthma Treatment (BOAT)	Patient	Oakland/Richmond CA, San Francisco CA, Portland Oregon, and Honolulu, Hawaii;	Kaiser Permanente "medical centers"	36 (measures were obtained 12 months prior to intervention and 24 months post-intervention)	Gov't
Wolever et al., 2010[66] NA	Patient	North Carolina	Duke University School of Medicine	6	Pharma

Author, Year Trial Name	Level of Randomization	Setting: Geography	Healthcare Setting	Study Duration (Months)	Funding Source
Zhang et al., 2010[67] NA	Other	Pennsylvania	Administrative data from enrollees in Medicare Advantage products offered by a large insurer	48	Multiple

Table D4. Intervention's disease focus, goal, and theoretical model

Author, Year Trial Name	Name of Disease or Condition	Specify Other Dx or Combinations of Dx	Goal of Intervention	What was the Target of the Intervention	Theoretical Model
Bender et al., 2010[1] NA	Asthma	NA	to improve adherence to controller medications among adults with asthma	Patient	Other
Berg et al., 1997[2] NA	asthma	NA	use a nurse-administered asthma self-management program to improve compliance, asthma symptoms, and airway obstruction among patients in a rural setting	Patient	Self-efficacy theory
Berger et al., 2005[3] NA	Multiple sclerosis		Decrease discontinuation of Avonex	Patient	Transtheoretical Model of Change (stages of change)
Bogner et al., 2008[4] NA	Depression	Hypertension	(1) fewer depressive symptoms, (2) lower systolic BP and diastolic BP, (3) a greater proportion with 80% or greater adherence to an antidepressant medication, and (4) a greater proportion with 80% or greater adherence to an antihypertensive medication	Patient	Other
Bogner et al., 2010[5] NA	Multiple chronic conditions	Diabetes and depression	Adherence Goals: To increase the proportions of participants with ≥80% adherence to an oral hypoglycemic agent and ≥80% adherence to an antidepressant at 6 weeks, compared to usual care Clinical Goals: To increase the proportion of participants with lower amounts of glycosylated hemoglobin in their blood and fewer depressive symptoms, compared to usual care	Patient	Other
Bosworth et al., 2005[6] V-STITCH	Hypertension	NA	To promote adherence with medication and improve health behaviors	patient	Prospect Theory

Author, Year Trial Name	Name of Disease or Condition	Specify Other Dx or Combinations of Dx	Goal of Intervention	What was the Target of the Intervention	Theoretical Model
Bosworth et al., 2008[7] TCYB Bosworth et al., 2007[8] TCYB Methods paper	Hypertension	NR	To promote medication adherence and improve hypertension-related health behaviors	patient	Transtheoretical Model of Change (stages of change)
Capoccia et al., 2004[9] na	Depression	NA	Improving quality of care and out-comes to patients diagnosed with a new episode of depression.	patient	Other
Carter et al., 2009[10] NA	Hypertension	NA	To achieve better guideline adherence, lower mean BP, higher rates of BP control, and higher rates of medication adherence to antihypertensives	Patient, pharmacists, MDs	
Chernew et al., 2008[11] NA	Multiple chronic conditions	Diabetes, hyperlipidemia, *hypertension*	Improve medication adherence	Patient	Other
Choudhry et al., 2010[12] NA	Multiple chronic conditions	Diabetes, hypercholesterolemia, coronary artery disease, congestive heart failure, hypertension	To improve medication adherence to statins & clopidogrel among company employees & beneficiaries with diabetes or vascular disease by eliminating copayments for statins and lowering copayments for all employees & beneficiaries prescribed clopidogrel	Patient & policy	Other
Choudhry et al., 2011[13] MI FREEE	Myocardial Infarction	NA	Increase adherence to medications and improve outcomes after myocardial infarction	Policy	None
Friedman et al., 1996[14] NA	Hypertension	heart disease, stroke, diabetes, and other (see baseline characteristics)	monitoring BP and treatment and counseling patients to be adherent	patient	Other
Fulmer et al., 1999[15] NA	Congestive Heart Failure		Increase the proportion of prescribed cardiac medications taken by these patients	patient	Other
Grant et al., 2003[16] NA	Diabetes	NS	1. Increase medication adherence rates by identifying and reducing barriers; 2. identify and reduce discrepancies between patient-reported and physician-documented medication regimens	patient and physician	Other

Author, Year Trial Name	Name of Disease or Condition	Specify Other Dx or Combinations of Dx	Goal of Intervention	What was the Target of the Intervention	Theoretical Model
Guthrie et al., 2001[17] First Myocardial Infarction (MI) Risk Reduction Program	Elevated cholesterol	at increased risk for first MI	To examine adherence to medication regimens and to recommendations to modify lifestyle risk factors in patients at risk for a first MI	patient	Other
Hoffman et al., 2003[18] NA	Depression	NA	To increase antidepressant medication adherence	Patient	Other
Hunt et al., 2008[19] NA	Hypertension	See baseline characteristics	Goal of the study: assess the impact of physician-pharmacist team-base care on BP control, quality of life, and patient satisfaction in patients cared for by all physicians practicing in multiple community-based clinics.	Patient	Other
Janson et al., 2009[21] NA	Asthma	NA	self-management education to improve long-term adherence to inhaled corticosteroid (ICS) therapy and markers of asthma control	patient	Other
Janson et al., 2003[20] NA	asthma	NA	use individual self-management education= to improve adherence to anti-inflammatory medication, biological markers of airway inflammation, and clinical outcomes	patient	Other
Johnson et al., 2006[22] NR	Elevated cholesterol	NR	To provide individualized guidance to improve medication adherence, moderate exercise, and low fat diet	patient	Transtheoretical Model of Change (stages of change)
Johnson et al., 2006[23] NR	Hypertension	NA	To overcome limitations to medication adherence by delivering individualized, theoretically derived interventions for entire populations of individuals, including those who may not be motivated to change	patient	Transtheoretical Model of Change (stages of change)
Katon et al., 1995[24] NA	Depression	NA	improve treatment of depression to the level recommended by practice guidelines	patient, provider, and structure of delivery of care	Other
Katon et al., 1996[25] NA	Depression	NR	To improve the management of depression in primary care	patient, provider, and system	Other

Author, Year Trial Name	Name of Disease or Condition	Specify Other Dx or Combinations of Dx	Goal of Intervention	What was the Target of the Intervention	Theoretical Model
Katon et al., 1999[26] NA Katon et al., 2002[27] NA	Depression	NA	To improve antidepressant medication adherence; severity of depressive symptoms and functional impairment.	Patient & provider	Other
Katon et al., 2001[28] NA Ludman et al., 2003[29] NA Van Korff et al., 2003[30] NA	Depression	NA	to prevent depression relapse; improve adherence to antidepressant medication; determine whether increased adherence is associated with less depressive symptoms and relapse/recurrence of major depressive episodes; and to increase self-efficacy and behavioral skills for self-management of depression	patient, provider	Social Cognitive Theory (self-efficacy)
Lee et al., 2006[31] FAME	Not Specified	NR	To improve medication adherence, BP, and LDL cholesterol for a population at increased risk for medication non-adherence	Patient	Other
Lin et al., 2006[32] NA	Diabetes	Depression	To improve diabetes self-care behaviors, including adherence to diabetes medications, by improving depression treatment	Patient	Other
Maciejewski et al., 2010 [33] NA	Multiple chronic conditions	Diabetes, HTN, hyperlipidemia, congestive heart failure	To improve medication refill adherence over a one-year period	Policy	NA
Mann et al., 2010[34] The Statin Choice	Diabetes	NS	To improve perceived risk of heart attack and medication adherence to statins of patients with diabetes.	Patient	Other
Montori et al., 2011[35] NA	Osteoporosis	NA	Improve adherence to osteoporosis treatment	Patient	None
Murray et al., 2007[36] NA	Congestive Heart Failure	NA	To determine whether a pharmacist intervention improves medication adherence and health outcomes compared with usual care for low-income patients with HF.	Patient	NR

Author, Year Trial Name	Name of Disease or Condition	Specify Other Dx or Combinations of Dx	Goal of Intervention	What was the Target of the Intervention	Theoretical Model
Nietert et al., 2009[37] NA	Multiple chronic conditions	Diabetes, hypertension, hyperlipidemia, heart failure, depression, psychosis	To improve pharmacy medication refill rates for 1 of 6 chronic diseases among patients identified as being overdue for their prescriptions	Patient	Other
Okeke et al., 2009[38] NA	Glaucoma	Could also be glaucoma suspect or have ocular hypertension (rather than having glaucoma diagnosis)	Improve adherence with topical, once daily glaucoma medication	Patient	
Pearce et al., 2008[39] Cardiovascular Risk Education and Social Support (CaRESS) Trial	Diabetes	NA	To educate, motivate, and facilitate patients and their support persons to work together to improve the patients' cardiovascular risk, health-related quality of life, and satisfaction with health care	Patient	Health Belief Model
Powell et al., 1995[40] NA	Multiple chronic conditions	Hypertension, hyperlipidemia	To improve medication adherence by enhancing patients' knowledge about their disease/condition and their prescribed treatment for it	Patient	Other
Powers et al., 2011[68] NA	Hypertensio n	Cardiovascular heart disease	Evaluate the impact of personalized CHD and stroke risk communication on patients' knowledge, beliefs, decision making, and health behaviors	Patient	NA
Pyne et al., 2011[41] HIV Translating Initiatives for Depression Into Effective Solutions (HITIDES)	Depression	HIV	Apply collaborative care of depression model to HIV settings for: improved depression severity, health-related QOL, health status, HIV symptom severity, and medication regimen adherence	intervention targeted at patients and providers: educated patients, made treatment recommendations for providers	Other
Rich et al., 1996[42] NA	Congestive Heart Failure	NA	To use a multidisciplinary approach to improve medication compliance rates among the elderly with congestive heart failure	patient	Other

Author, Year Trial Name	Name of Disease or Condition	Specify Other Dx or Combinations of Dx	Goal of Intervention	What was the Target of the Intervention	Theoretical Model
Rickles et al., 2005[43] NA	Depression	NA	(1) Greater frequency of patient feedback to pharmacist, (2) fewer missed antidepressant (AD) doses, (3) greater AD knowledge, (4) more positive AD beliefs, (5) a more positive orientation toward treatment progress, and (6) greater improvement in depression symptoms.	patient	Other
Ross et al., 2004[44] NR	Congestive Heart Failure	NA	To improve self-efficacy, adherence, satisfaction, and possibly health status	combination [patient, system]	Other
Rudd et al., 2009[46] NA	Inflammatory Arthritis	Also included patients with rheumatoid arthritis and psoriatic arthritis	To test how effective educational interventions are in reducing barriers to literacy and improve outcomes including medication adherence in patients with inflammatory arthritis	Patient	
Rudd et al., 2004[45] NA	Hypertension	NA	To increase patient education and frequent home BP monitoring	Combination [patient, system of care]	Social Cognitive Theory (self-efficacy)
Schaffer et al., 2004[47] NA	asthma	NA	The study primarily compared the effects of a theoretically focused audiotape or a standard educational booklet, or both of these, on adherence to asthma preventive medication.	Patient	Protection Motivation Theory
Schectman et al., 1994[48] NA	Elevated cholesterol	NA	To improve patient adherence and tolerance to niacin and BAS therapy	Patient	Other
Schneider et al., 2008[49] NA	Hypertension	N-A	Improve adherence and clinical outcomes	Patient	
Schnipper et al., 2006[50] NA	Other		Reduce the rate of preventable adverse drug events	System, patient	
Simon et al., 2006[51] na	Depression	NA	NR; however, implicitly it is to use low intensity phone care management system to diminish depressive symptoms and functional impairment with low insensitivity are	Patient and provider	Other
Sledge et al., 2006[52] NA	Other	N-A	Decrease inpatient readmission rates, reduce use of emergency services, reduce total costs, improve health outcomes (including adherence)	Patient, provider	

Author, Year Trial Name	Name of Disease or Condition	Specify Other Dx or Combinations of Dx	Goal of Intervention	What was the Target of the Intervention	Theoretical Model
Smith et al., 2008[53] NR	Myocardial Infarction	NR	To promote adherence to Beta-blocker therapy following MI	Patient and providers	Other
Solomon et al., 1998[54] na Gourley et al., 1998[55] NA	Chronic Obstructive Pulmonary Disease	Hypertension	To improve compliance to medication regimen, satisfaction with care, knowledge about disease and management, and quality of life in the intervention group compared to the control group.	Patient	Other
Stacy et al., 2009[56] NA	Elevated cholesterol	NA	To increase statin Adherence/persistence by enhancing both intrinsic motivations for medication persistence and self-management.	patient	Transtheoretical Model of Change (stages of change)
Taylor et al., 2003[57] NA	Other	Multiple Conditions	Improve the prevention, detection, and resolution of drug-related problems.	Patient, provider	Other
Vivian et al., 2002[58] NA	Hypertension	NA	To determine whether a pharmacist-managed hypertension clinic improves treatment outcomes (medication compliance, BP control, diabetes control, patient satisfaction, quality of life) in patients with hypertension	patient	Other
Waalen et al., 2009[59] NA	Osteoporosis	N-A	improve use of medication 1 year after prescription	Patient	
Wakefield et al., 2011[60]	Diabetes	Hypertension	To improve outcomes in veterans with comorbid DM and HTN	Patient	NA
Weinberger et al., 2002[61] NA	Other	asthma and COPD	not stated, but implicitly to use a pharm care to improve patients' peak expiratory flow rate (PEFR), health-related quality of life (HRQOL), medication compliance, and to decrease breathing-related emergency department (ED) or hospital visits; also to increase patient satisfaction with care and with their pharmacist	provider (i.e. pharmacist), but outcomes measured at patient level	Other

Author, Year Trial Name	Name of Disease or Condition	Specify Other Dx or Combinations of Dx	Goal of Intervention	What was the Target of the Intervention	Theoretical Model
Weymiller et al., 2007[62] Statin Choice Randomized Trial Jones et al., 2009[63] Statin Choice Randomized Trial	Diabetes	NA	To estimate the extent to which the Statin Choice decision aid compared with usual care plus a standard pamphlet was acceptable to patients, could improve patient knowledge, and reduced decisional conflict in choosing whether or not to use a statin To test the hypothesis that improvements in the conversations between patients and their clinicians about therapy can enhance adherence.	Patient	Other
Williams et al., 2010[64] NA	asthma	NA	Implicit - to improve patient adherence to ICS by facilitating the provision of adherence feedback from physicians	Providers were targeted but outcomes measured among patients	Other
Wilson et al., 2010[65] Better Outcomes of Asthma Treatment (BOAT)	Asthma	NA	SDM approach would exhibitgreater adherence to controller medications, better asthma-related quality of life, and lower health care utilization for acutesymptoms than patients who received usual care (no asthmacare management);	Patient	Shared Decision Making
Wolever et al., 2010[66] NA	Diabetes	NA	To improve lifestyle behaviors, psychosocial functioning, and A1C	Patients	Other
Zhang et al., 2010[67] NA	Multiple chronic conditions	NA	Medicare Part D was intended to reduce the burden of high drug costs on the elderly and to reduce the underuse of medication due to cost.	Patient	Other

Table D5. Inclusion and exclusion criteria

Author, Year Trial Name	Inclusion Criteria	Exclusion Criteria
Bender et al., 2010[1] NA	Fifty 18- to 65-year-old adults who had physician-diagnosed asthma for which they were prescribeddaily inhaled corticosteroid treatment participated.Participants were recruited through newspaper advertising and in cooperation with community allergy practices and they received $25 for each completed study visit.	(1) Any significant disease or disorder that, in the opinion of the investigator, might influence the results of the study or the patient's ability to participate in the study (this included other chronic health disorders, current substance abuse or dependence, mental retardation, or psychiatric disorder); and (2) current participation in any other asthma-related research or clinical trial.
Berg et al., 1997[2] NA	18 years of age and older with a medical diagnosis of asthma who were being treated with prescribed, regularly administered, inhaled medications other than as-needed bronchodilators;	those with other respiratory disorders (i.e. other than asthma) or were current smokers were excluded
Berger et al., 2005[3] NA	Currently using Avonex	NR
Bogner et al., 2008[4] NA	(1) aged 50 years and older; (2) a systolic BP of 140 mm Hg or greater or diastolic BP of 90 mm Hg or greater for nondiabetic patients, or a systolic BP of 130 mm Hg or greater or a diastolic BP of 80 mm Hg or greater for patients with diabetes on at least 2 visits in the previous year, or a prescription for an antihypertensive medication within the past year; and (3) a diagnosis of depression or a prescription for an antidepressant medication within the past year.	excluded: cognitively impaired, unable to communicate in English, resided in a care facility that provides medications on a schedule, and unable to use Medication Event Monitoring System (MEMS) caps
Bogner et al., 2010[5] NA	Ages 50 and older An A1C >7 at their last primary care office visit or a prescription for an oral hypoglycemic agent within the past year A diagnosis of depression or a prescription for an antidepressant within the past year	Presence of mania or hypomania, psychotic syndrome, alcohol abuse or dependence, acutely suicidal or psychotic thoughts, cognitive impairment, residing in a care facility that provided medications on schedule, or inability/unwillingness to use the Medication Event Monitoring System (MEMS)
Bosworth et al., 2005[6] V-STITCH	Diagnosis of hypertension by outpatient ICD diagnostic code on outpatient encounter forms, enrolled in Durham VAMC primary care clinic, prescription of hypertensive medication (ACE inhibitors, beta blockers, calcium channel blockers, diuretics, alpha1 blockers, and/or central alpha2 agonists) in the previous year	NR

Author, Year Trial Name	Inclusion Criteria	Exclusion Criteria
Bosworth et al., 2008[7] TCYB Bosworth et al., 2007[8] TCYB Methods paper	Seen in one of the two primary care clinics for at least one year; had a diagnosis of hypertension by outpatient diagnostic code; using a hypertensive medication at the time of baseline visits	not using or prescribed BP medication; spouse participating in study; not living in a surrounding eight county catchment area; receiving kidney dialysis; received organ transplant; planning a pregnancy; hospitalized for stroke; MI; coronary artery revascularization; diagnosis of metastatic cancer in prior 3 months; dementia diagnosis; resident of nursing home or receiving home health care; arm size too large for home BP monitor cuff; severely impaired hearing or speech
Capoccia et al., 2004[9] na	The initial screening included an assessment for depression using the Primary Care Evaluation of Mental Disorders (PRIME-MD13) and two questionnaires to evaluate inclusion and exclusion criteria and alcohol use (Alcohol Use Disorders Identification Test [AUDIT])	Exclusion criteria included (1) age of <18 years, (2) terminal illness, (3) psychosis, (4) recent (within the past 3 months) alcohol (AUDIT score of >8) or substance abuse, (5) two or more suicide attempts, (6) pregnancy or nursing, (7) limited command of the English language, and (8) unwillingness to use UWFMC as a source of care for the next 12 months.
Carter et al., 2009[10] NA	Males or females over 21 years of age; Diagnosis of essential hypertension; Taking 0-3 antihypertensives; Patients without a diagnosis of diabetes :systolic BP (SBP) between 140-179 mm Hg or diastolic BP (DBP) 90-109 mm Hg; Patients with diabetes: SBP between 130-179 mm Hg or DBP 80-109 mm Hg	BP medication or dose change within 4 weeks of baseline visit; Stage 3 hypertension (Bp> 180/110 mm Hg); Evidence of hypertensive urgency or emergency; Myocardial infarction or stroke within 6 months prior to screening; New York Heart Association class III or IV heart failure; Unstable angina; Serious renal or hepatic disease; Pregnancy; Poor prognosis (life expectancy < 3 years); Dementia; Cognitive impairment
Chernew et al., 2008[11] NA	Employees and dependents ages 18 - 64 years who were continuously enrolled for the relevant quarter and the entire previous quarter.	Age $\geq$65
Choudhry et al., 2010[12] NA	For the statin cohort: Filled a statin prescription between January 1, 2006, & December 31, 2007; Diagnosis of diabetes or vascular disease For the clopidogrel cohort: Filled a clopidogrel prescription during the same time period as required for inclusion in the statin cohort	NR
Choudhry et al., 2011[13] MI FREEE	Received both medical and prescription drug benefits through Aetna, discharged from hospital with principal or secondary diagnosis code of ICD-9-CM 410 (except when the 5th digit was 2) and a length of stay of 3-180 days.	Enrolled in a health savings account, age ≥65 at time of hospital discharge
Friedman et al., 1996[14] NA	$\geq$60 years, under the care of a physician for hypertension, be prescribed antihypertensive medication, have a systolic Bp>160 mm Hg or diastolic Bp> 90 mm Hg based on an average of two determinations taken 5 minutes apart.	Diagnosis of a life threatening illness, not English speaking, did not have a telephone or could not use one, or refusal to participate.

Author, Year Trial Name	Inclusion Criteria	Exclusion Criteria
Fulmer et al., 1999[15] NA	Patient of the 2 recruitment sites; primary or secondary diagnosis of CHF; ≥65 years old; resident of Manhattan; no pre-pour medications order; use of an ACE inhibitor, calcium channel blocker, or beta-blocker; fluency in English or Spanish; experience in using a phone; Mini Mental-Status Examination score ≥20; home equipped with phone and modular phone jack; home not in high-crime building requiring security guard accompaniment for study staff	NR
Grant et al., 2003[16] NA	1. Type 2 Diabetes Mellitus in claims data confirmed by physician diagnosis found in the medical record during structured chart review; 2. At least one HbA1c and one cholesterol level measured in year before the study; 3. At least one clinic visit in the 6 months preceding the study	1. Terminal illness per medical record; 2. Cognitive deficit per medical record; 3. could not communicate in spoken English
Guthrie et al., 2001[17] First Myocardial Infarction (MI) Risk Reduction Program	Patients with risk scores >/=4 on a scale of -1 to +16 for men and -1 to +17 for women on the First Heart Attack Risk Test reflecting increased risk of a first MI, elevated total cholesterol despite dietary intervention	Previous MI, current therapy with a statin, membership in a federally funded health care program (except Medicare or plans for federal employees), Medicaid patients, women of childbearing potential
Hoffman et al., 2003[18] NA	Patients over 18 years of age who were newly prescribed antidepressant drug therapy (defined as a prescription claim for antidepressant drug within the last 30 days, with no record of claims for an antidepressant for the 6 months previous to that time); and to have continuous enrollment during the pretreatment period (6 months before) and for at least 12 months after the initial prescription identification.	Excluded if: prescribed combination antidepressant and anxiolytic-type medications; taking clomipramine or fluvoxamine; received one of the following concomitant medications within 120 days before the antidepressant prescription: valpric acid, carbamazepine, lithium, or lamotrigine.
Hunt et al., 2008[19] NA	Patients with known hypertension, an office visit within the past 2 years, a last systolic Bp>160 mmHg and/or a last diastolic Bp>100 mmHg.	No BP reading in chart in the previous 2 years, had attended a visit with a pharmacy practitioner in the previous 6 months, or had transferred care out of network.
Janson et al., 2009[21] NA	18 to 55 years of age with moderate-to-severe persistent asthma (i.e., FEV1 <80% of predicted value, daily symptoms, and 1 nighttime awakening per week), were nonsmokers with 5 or less pack-years of smoking history, and demonstrated spirometric evidence of reversible air flow obstruction or bronchial reactivity to inhaled methacholine	received systemic steroids within 4 weeks of study enrollment; with upper respiratory tract infection within 6 weeks of enrollment, pregnancy, or cardiac, gastrointestinal, psychiatric, or other lung disease; or with prior participation in a formal asthma education program; nonreversible airflow obstruction; current smokers

Author, Year Trial Name	Inclusion Criteria	Exclusion Criteria
Janson et al., 2003[20] NA	History of physician-diagnosed asthma; age between 18 and 55 years; nonsmoking (lifetime smoking history 5 pack-years; none in the last year); and bronchial hyper-responsiveness to inhaled methacholine (concentration causing a 20% fall in forced expiratory volume in 1 second [FEV1] of 8 mg/mL). Subjects with baseline FEV1 60% predicted, 20% variability, or fall in FEV1 with diluent did not undergo methacholine challenge	treatment with oral corticosteroids within 4 weeks; upper respiratory tract infection within 6 weeks; lung disease other than asthma; pregnancy; history of cardiac, gastrointestinal, or psychiatric disease; or prior participation in a formal asthma education program
Johnson et al., 2006[22] NR	between ages 21 and 85; prescribed cholesterol medication currently; able to read and speak English	NR
Johnson et al., 2006[23] NR	between ages 18 and 80; prescribed medication to treat hypertension; able to read and speak English; not in the maintenance (M) stage of change once the quota for M was reached	excluded by provider
Katon et al., 1995[24] NA	20-item symptom checklist depression screening score ≥0.75; age 18-80; willing to take anti-depressant medication; diagnosed by PCP as meeting criteria for definite or probable major depression	CAGE score ≥2; current psychotic symptoms or suicidal ideation; dementia; pregnancy; terminal illness; limited command of English; plan to dis-enroll from the medical center insurance plan within next 12 months
Katon et al., 1996[25] NA	Patients who were diagnosed with definite or probable major depression and who agreed to initiate antidepressant therapy were screened for eligibility. Eligibility was based on 1) a 20-item depression symptom checklist score of 0.75 or greater, 2) age 18 to 80 years, and 3) willingness to take antidepressant medication.	Current alcohol abuse (screening score of 2 or more on the CAGE questionnaire; current psychiatric symptoms or serious suicide ideation or plan; dementia; pregnancy; terminal illness; limited command of English; and plan to withdraw from the insurance plan within next 12 months.
Katon et al., 1999[26] NA Katon et al., 2002[27] NA	Receipt of a new antidepressant prescription (no prescriptions within the last 120 days) for diagnosis of depression or anxiety; having 4 or more residual major depressive symptoms or having recurrent depression (2 or more prior episodes) or dysthymia	Screening score of 2 or more on the CAGE alcohol screening questionnaire, pregnant or currently nursing; planning to dis-enroll from the HMO within the next 12 months; currently seeing a psychiatrist; limited command of English; recently used lithium or antipsychotic medication

Author, Year Trial Name	Inclusion Criteria	Exclusion Criteria
Katon et al., 2001[28] NA Ludman et al., 2003[29] NA Van Korff et al., 2003[30] NA	1) Remission of the index of depressive episode (defined as either less than 4 of the 8 DSM-IV depression criteria or four DSM-IV criteria with an SCL depression score <1.0; and 2) high risk of relapse (defined as a history of 3 or more lifetime depressive episodes or a history of dysthymic disorder.	2+ score on the CAGE alcohol questionnaire, plans to dis-enroll from HMO within 12 months, recent use of mood stabilizer or antipsychotic medication, pregnancy or nursing, and current medication management by a psychiatrist, limited command of English, and recently using lithium or antipsychotic medication
Lee et al., 2006[31] FAME	elderly men and women (>=65 years old); taking 4 or more chronic medications daily	did not live independently (assisted living or nursing home residents); presence of any serious medical condition for which 1 year survival was expected to be unlikely
Lin et al., 2006[32] NA	Aged 18 years or older Enrolled in a Group Health Cooperative health plan At least 2 fasting plasma glucose levels of >126 mg/dL or a random plasma glucose level of >200 mg/dL Current use of any diabetic medications Inpatient or outpatient diagnosis of diabetes Score of 10 or higher on the PHQ-9 and a score of 1.1 or higher on the SCL-20 indicating persistent depression.	Not having diabetes Having gestational diabetes Cognitive impairment Terminal illness Disenrollment or planned disenrollment from the health plan Language or hearing barrier Psychotic disorder Bipolar disorder Use of mood-stabilizing or antipsychotic medication except those on anti-depressant allowed if still had persistent depressive symptoms. Current care by a psychiatrist
Maciejewski et al., 2010 [33] NA	People enrolled with the insurer (BCBSNC) for the entire study period and were taking a medication from at least 1 of the 8 drug classes evaluated	See inclusion criteria
Mann et al., 2010[34] The Statin Choice	All adult English or Spanish speaking primary care patients with a diagnosis of diabetes.	NR
Montori et al., 2011[35] NA	Women who were postmenopausal, age ≥50, bone mineral density levels consistent with osteopenia or osteoporosis, not already taking bisphosphonates or other osteoporosis medication (other than vitamin D and calcium), found eligible for bisphosphonate therapy by their clinician and had a follow-up appointment with that clinician, available for phone follow-up at 6 months	Inability to read English, major learning barriers impeding ability to provide consent or use the decision aid

Author, Year Trial Name	Inclusion Criteria	Exclusion Criteria
Murray et al., 2007[36] NA	1) 50 yrs of age or older 2) Planned to receive all of their care, including prescribed medications, at Wishard Health Services 3) Diagnosis of heart failure confirmed by primary care physician 4) Regularly used at least 1 cardiovascular medication for HF, including any of the following: ACE inhibitor/ARB, beta-blocker, diuretic, digoxin, aldosterone antagonist 5) Not using or planning to use medication container adherence aid (pill box) 6) Access to a working telephone 7) Could hear within range of a normal conversation	1) Dementia
Nietert et al., 2009[37] NA	Had a prescription written for diabetes mellitus, hypertension, hyperlipidemia, heart failure, depression, and/or psychoses; Had at least 2 refills remaining for at least a 30 days' supply	NR
Okeke et al., 2009[38] NA	Patients had diagnosis of open angle glaucoma, angle-closure glaucoma, glaucoma suspect, or ocular hypertension; ≥18 years old; using or prescribed a topical prostaglandin analog; able to return for 3- and 6-month follow-up visits; ≤75% adherence to eye drops during phase 1 of the study--a 3-month observational cohort.	Not able to understand the study, did not instill their own drops, incapable of using the dosing aid.
Pearce et al., 2008[39] Cardiovascular Risk Education and Social Support (CaRESS) Trial	At least 21 years old and able to give informed consentEither type 2 diabetes based on chart review according to American Diabetes Association diagnostic criteria or the diagnosis of type 2 diabetes recorded by the PCP along with a HbA1C level $\geq$8.0%, random serum glucose level >200 mg/dL, or current prescription for an antidiabetic drug Hypertension with suboptimal control, with or without uncontrolled dyslipidemia Prepared to designate a support person with whom the patient would be in contact for the next 12 monthsNot pregnant or planning to become pregnant within the next 12 months Planning to be available for follow-up for at least the next 12 months	NS
Powell et al., 1995[40] NA	A member of a specific large Midwestern HMO (i.e., receiving medical & prescription drug coverage through the plan); Had a pharmacy claim for benazepril, metoprolol, simvastatin, or transdermal estrogen	NR

Author, Year Trial Name	Inclusion Criteria	Exclusion Criteria
Powers et al., 2011[68] NA	Enrolled in primary care for at least 1 year; age ≥55 years; diagnosis of hypertension; received a prescription for hypertensive medication in previous year; systolic blood pressure >140 or diastolic blood pressure >90 based on their most recent blood pressure measurement within last 12 months; and had electrocardiogram within the last 5 years to evaluate the absence or presence of left ventricular hypertrophy	Hospitalized for a MI or coronary artery revascularization or had a diagnosis of metastatic cancer in the past 6 months; had a history of stroke; had active diagnosis of psychosis or dementia documented in medical record; were participating in another chronic disease self-management study; were resident of a nursing home; or did not have access to a telephon
Pyne et al., 2011[41] HIV Translating Initiatives for Depression Into Effective Solutions (HITIDES)	Providers: doesn't address provider participation - not clear if all providers at participating clinics enrolled in the study Participants: (1) a current 9-item Patient Health Questionnaire (PHQ-9) depression score of 10 or higher and (2) current treatment in the VA HIV clinic. A PHQ-9 score of at least 10 has strong psychometric properties in primary care settings (e.g., 99% sensitivity and 91% specificity).	(1) No access to a telephone, (2) current acute suicidal ideation, (3) significant cognitive impairment as indicated by a score higher than 10 on the Blessed Orientation-Memory-Concentration Test, and (4) history of bipolar dis-order or schizophrenia.
Rich et al., 1996[42] NA	Patients aged 70 years or older who were admitted to a university teaching hospital with congestive heart failure as defined by presence of typical symptoms (e.g. exertional dyspnea, orthopnea, impaired activity tolerance) and physical findings (elevated jugular venous pressure, pulmonary rales, S3 gallop, dependent edema), in conjunction with radiographic evidence of pulmonary congestion and a favorable response to diuresis.	severe dementia defined as inability to assist with self-care, other life-threatening illnesses, patients discharged to long-term care facility
Rickles et al., 2005[43] NA	no antidepressant use in the past 4months, were 18 years or older, were willing to pick up theirantidepressant from a study pharmacy during the next 4 months, had no hearing impairment, and planned to be in the local area during the next 4 months.	Excluded if Beck Depression Inventory (BDI-II) score below 16, required a translator, were pregnant or nursing, were receiving medications for a psychotic or bipolar disorder, and/or had physical conditions requiring additional caution with their antidepressant.
Ross et al., 2004[44] NR	patients of a specialty clinic for heart failure at University of Colorado Hospital; spoke English; 18 years old or older; use of Web browser before	physicians, nurses, physician assistants, nurse practitioners
Rudd et al., 2009[46] NA	Patients with rheumatoid arthritis, psoriatic arthritis, and inflammatory arthritis; had ≥1 visit with rheumatologist (the rheumatologist must have consented to helping with the study)	<18 years old; medical professionals; post-graduate degree; visual impairment affecting reading ability; non-English-speakers
Rudd et al., 2004[45] NA	Eligible for hypertensive drug therapy according to JNC VI criteria (presence of coronary risk factors, age>60 years, or a family history of premature cardiovascular disease or target organ damage); mean of two BP values >=150/95 mmHg on two screening visits conducted on separate days at least 1 week apart	NR

Author, Year Trial Name	Inclusion Criteria	Exclusion Criteria
Schaffer et al., 2004[47] NA	NR	NR
Schectman et al., 1994[48] NA	patients with hyperlipidemia requiring treatment with either niacin or BAS; did not previously take or currently taking niacin or BAS; access to a telephone	NR
Schneider et al., 2008[49] NA	≥65 years old, diagnosis of essential hypertension	cognitive impairment, visual impairment, severe arthritis, terminal illness that may result in death or impairment during study
Schnipper et al., 2006[50] NA	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	NR
Simon et al., 2006[51] na	aged 18 years or Older, received a new antidepressant prescription from a psychiatrist (that is, no antidepressant use in the past 90 days according to computerized pharmacy data), received a visit diagnosis of a depressive disorder in the past 30 days, and had no recorded diagnosis of bipolar disorder or schizophrenia in the past two years.	Exclusion criteria Assessed during the baseline interview included a score on the SCL depression scale that was less than .5 (that is, remission of depression), regular use of antidepressant medication in the prior 90 days (that is, the index prescription was not actually a new prescription), and cognitive, language, or hearing impairment severe enough to preclude participation
Sledge et al., 2006[52] NA	≥18 years old, ≥2 medical or surgical hospital admissions during eligibility phase (12m prior to patient selection efforts)	Outliers who had hospital cost greater than 2 SDs of log transformed mean total cost, Charlson Comorbidity Index >5
Smith et al., 2008[53] NR	Discharge diagnosis of MI (International Classification of Diseases, Ninth Revision codes 410.xx) between December 1, 2003 (start of enrollment), and June 18, 2004 (end of enrollment), who were at least 18 years old and had a beta blocker prescription dispensed (first beta blocker prescription was the index) before June 18, 2004, health plan and prescription eligibility and to have survived between MI and intervention mailing	Died or lost health plan eligibility before intervention and during follow-up period

Author, Year Trial Name	Inclusion Criteria	Exclusion Criteria
Solomon et al., 1998[54] na Gourley et al., 1998[55] NA	For both groups: - could read and write English- signed informed consent- able to understand the study proceduresHypertension group:- currently receiving dihydropyridine therapy or dihydropyridine and diuretic therapy for hypertension- 18 years of age or olderCOPD group:- ambulatory COPD patient at the institution- received pulmonary function tests to document a diagnosis of COPD- currently being treated for a diagnosis of COPD per American Thoracic Society criteria- currently receiving a pharmacotherapeutic regimen that included at least one metered dose inhaler for treatment of COPD- mentally and physically capable of using an MDI/spacer inhaler- 40 years of age or older- had access to a telephone	For both groups:- evidence of alcohol or drug abuse within the past year that would likely interfere with performance of the study- refused to give informed consent- had participated in any investigational drug trial within 30 days prior to enrollment or was scheduled to participate in any other study during conduct of the trialHypertension group:- symptomatic heart failure- currently taking any antihypertensive agent other than a dihydropyridine or a diureticCOPD group:- a history of severe, life-threatening COPD defined as a history of mechanical ventilation during the past year or a life expectancy of <6 months- had been hospitalized or had visited the emergency department during the past two weeks- had a lung infection in the two weeks prior to enrollment- decompensated congestive heart failure Class III or IV- had been diagnosed with any other lung disease except for concomitant asthma
Stacy et al., 2009[56] NA	recently filled a prescription for a Statin, continuously enrolled in the plan with a pharmacy benefit for a minimum of 12 months prior to the date of the index statin; no pharmacy claims evidence of any lipid-lowering agent in the 6-month period prior to the index statin; 21 years of age or older; a statin prescription with a 30-day supply; remained continuously enrolled in plan with a pharmacy benefit for a minimum of 6 months after index statin date	NR
Taylor et al., 2003[57] NA	Adult patients (18 years or older) who received care at the participating clinics and were identified as being at high risk for medication-related adverse events (presence of three or more of the following risk factors: five or more medications in the drug regimen, 12 or more doses per day, four or moremedication changes in the previous year, three or more concurrent diseases, a history of medication noncompliance,and the presence of drugs requiring therapeutic monitoring)	Significant cognitive impairment, a history of missed office visits, scheduling conflicts, or a life expectancy of lessthan one year
Vivian et al., 2002[58] NA	older than 18 years old; confirmed diagnosis of essential hypertension (systolic Bp>140 mmHg or diastolic Bp>90 mmHg), receiving antihypertensive drug therapy (and BP>140/90 mmHg), receiving all drugs from a Veterans Affairs Medical Center pharmacy, not receiving care at the pharmacist-managed clinic until the study began	secondary cause of hypertension such as chronic renal disease, renovascular disease, pheochromocytoma, Cushing's syndrome, and primary aldosteronism; missed more than 3 appointment in the last year; in hypertensive crisis, diagnosis of NYHA class III or IV chronic heart failure, end-stage renal disease, a psychiatric disorder, severe hepatic dysfunction, terminal cancer, or other condition that limited life expectancy to less than a year
Waalen et al., 2009[59] NA	Female, ≥60 years old, had uncomplicated osteoporosis (per National Osteoporosis Foundation guidelines), not previously identified as having osteoporosis	Secondary osteoporosis other than Vitamin D deficiency, unable to provide consent, spoke in a language precluding conversing with study staff

Author, Year Trial Name	Inclusion Criteria	Exclusion Criteria
Wakefield et al., 2011[60]	Coexisting DM and HTN, a landline telephone in the home, receipt of primary care from the VA in the previous 12 months, and anticipation of receiving primary care for the duration of study enrollment	Legally blind, resided in a long-term care facility, or who had diagnoses indicating dementia or psychosis
Weinberger et al., 2002[61] NA	Inclusion criteria for drugstores not described; Inclusion criteria for patients: filled a prescription formethylxanthines, inhaled corticosteroids, inhaled or oral sympathomimetics, inhaled parasympathetic antagonists, or inhaled cromolyn sodium during the preceding 4 months; (2) reported having COPD or asthma as an active problem; (3) were 18 years or older; (4) received 70% or more of their medications from a single study drugstore; (5) reported no significant impairment in vision, hearing, or speech that precluded participation; (6) did not reside in an institution (e.g., nursing home); and (7) provided written informed consent.	not reported
Weymiller et al., 2007[62] Statin Choice Randomized Trial Jones et al., 2009[63] Statin Choice Randomized Trial	Had type 2 diabetes Were referred to the clinic Had no contraindications to statin use Able (no major hearing, visual, or cognitive impairment or did not require translation) and willing to provide informed consent Available for follow-up at 3 months	NR
Williams et al., 2010[64] NA	Providers: Health system primary care providers (i.e., in the areas of family practice, internal medicine, and pediatrics) were invited to participate. Pt eligibility: a previous electronic prescription for an ICS between January 19, 2005, and April 30, 2007; age 5 to56 years as of April 30, 2007; continuous enrollment in the affiliated health maintenance organization (HMO) for at least 1 year before April 30, 2007; prescription drug coverage as of April 30, 2007; at least 1 physician diagnosis of asthma and at least 1 visit to a primary care provider in the year efore April 30, 2007. Patients meeting these criteria were invited by letter to participate in the study	Patient: diagnosis of chronic obstructive pulmonary or congestive heart failure after January 19, 2005;

Author, Year Trial Name	Inclusion Criteria	Exclusion Criteria
Wilson et al., 2010[65] Better Outcomes of Asthma Treatment (BOAT)	KP members, aged 18–70 years, with evidence suggestive of poorly controlled asthma, were identified at five clinical sites using computerized records of overuse of rescue medications (a controller/[controller 1 rescue medication] ratio <0.5 and at least three b-agonist dispensings in the past year) or a recent asthma-related emergency department (ED) visit or hospitalization.	Intermittent asthma (brief exacerbations or symptoms less thanonce/wk), primary diagnosis of chronic obstructive pulmonary disease or emphysema, insufficient pulmonary function reversibility (for ex-/currentsmokers and those without regular controller use), regular use of oralcorticosteroids, and current asthma care management.
Wolever et al., 2010[66] NA	Patients were required to be English speaking, at least 18 years of age, have a diagnosis of type 2 diabetes for at least 1 year, be taking oral diabetes medication for at least 1 year, and have medical and pharmacy benefits available to the study team	Exclusion criteria included dementia, Alzheimer's disease, schizophrenia, or other cognitive impairment that would preclude informed consent
Zhang et al., 2010[67] NA	Enrolled between January 2003 and December 2007 in Medicare Advantage products, had at least two claims with a diagnosis of hyperlipidemia, diabetes, or hypertension, and filled at least one prescription for the diagnosed condition (for diabetes, focused on patients taking oral diabetes medications), included patients also had to be continuously enrolled between 2004 and 2007, 24 months before and 24 months after Part D implementation.	NR

Table D6. Key Questions 1-3

Author, Year Trial Name	Relevant for KQ 1a?	Improvement in Medication Adherence?	Relevant for KQ 1b	Relevant for KQ 2a?	Improvement in Medication Adherence?	Relevant for KQ 2b	Relevant for KQ 3a?	Relevant for KQ 3b?
Bender et al., 2010[1] NA	Yes	Yes	No	No	NA	No	Yes	No
Berg et al., 1997[2] NA	Yes	Yes	Yes	No	NA	NA	Yes	NA
Berger et al., 2005[3] NA	Yes	Yes	No	No	NA	NA	Yes	No
Bogner et al., 2008[4] NA	Yes	Yes	Yes	No	NA	No	Yes	NA
Bogner et al., 2010[5] NA	Yes	Yes	Yes	No	NA	NA	No	No
Bosworth et al., 2005[6] V-STITCH	Yes	No	No	No	NA	No	Yes	No
Bosworth et al., 2008[7] TCYB Bosworth et al., 2007[8] TCYB Methods paper	Yes	Yes	No	No	NA	No	Yes	No
Capoccia et al., 2004[9] NA	Yes	No	No	No	NA	No	Yes	No
Carter et al., 2009[10] NA	Yes	No	Yes	No	NA	No	Yes	No
Chernew et al., 2008[11] NA	No	NA	NA	Yes	Yes	No	No	No
Choudhry et al., 2010[12] NA	No	NA	No	Yes	Yes	No	No	No
Choudhry et al., 2011[13] MI FREEE	No	NA	NA	Yes	Yes	Yes	Yes	No
Friedman et al., 1996[14] NA	Yes	Yes	Yes	No	NA	NA	Yes	No
Fulmer et al., 1999[15] NA	Yes	Yes	Yes	No	NA	NA	Yes	Yes, study comparison is of a single intervention characteristic (KQ3b results = KQ1/KQ2 results)
Grant et al., 2003[16] NA	Yes	No	No	No	NA	NA	Yes	No

Author, Year Trial Name	Relevant for KQ 1a?	Improvement in Medication Adherence?	Relevant for KQ 1b	Relevant for KQ 2a?	Improvement in Medication Adherence?	Relevant for KQ 2b	Relevant for KQ 3a?	Relevant for KQ 3b?
Guthrie et al., 2001[17] First Myocardial Infarction (MI) Risk Reduction Program	Yes	No	No	No	NA	No	Yes	No
Hoffman et al., 2003[18] NA	Yes	Yes	No	No	NA	NA	Yes	No
Hunt et al., 2008[19] NA	Yes	No	No	No	NA	NA	Yes	No
Janson et al., 2003[20] NA	Yes	Yes	Yes	No	NA	No	Yes	No
Janson et al., 2009[21] NA	Yes	Yes	Yes	No	NA	No	Yes	NA
Johnson et al., 2006[22] NR	Yes	Yes	No	No	NA	No	Yes	No
Johnson et al., 2006[23] NR	Yes	Yes	No	No	NA	No	Yes	No
Katon et al., 1996[25] NA	Yes	Yes	Yes	No	NA	NA	Yes	No
Katon et al., 1995[24] NA	Yes	Yes	Yes	No	NA	NA	Yes	No
Katon et al., 1999[26] NA Katon et al., 2002[27] NA	Yes	Yes	Yes	No	NA	NA	No	No
Katon et al., 2001[28] NA Ludman et al., 2003[29] NA Van Korff et al., 2003[30] NA	Yes	Yes	Yes	No	NA	NA	Yes	No
Lee et al., 2006[31] FAME	Yes	Yes	Yes	No	NA	No	Yes	No
Lin et al., 2006[32] NA	Yes	No	NA	No	NA	NA	Yes	No
Maciejewski et al., 2010[33] NA	No	NA	No	Yes	Yes	No	Yes	No
Mann et al., 2010[34] The Statin Choice	Yes	No	No	No	NA	No	Yes	NO

Author, Year Trial Name	Relevant for KQ 1a?	Improvement in Medication Adherence?	Relevant for KQ 1b	Relevant for KQ 2a?	Improvement in Medication Adherence?	Relevant for KQ 2b	Relevant for KQ 3a?	Relevant for KQ 3b?
Montori et al., 2011[35] NA	Yes	Yes	No	No	NA	No	Yes	No
Murray et al., 2007[36] NA	Yes	Yes, during months 1-9, then no in months 9-12 following intervention cessation	Yes	No	NA	NA	Yes	No
Nietert et al., 2009[37] NA	Yes	No	NA	No	NA	No	Yes	Yes, study comparison is of a single intervention characteristic (KQ3b results = KQ1/KQ2 results)
Okeke et al., 2009[38] NA	Yes	Yes	Yes	No	NA	NA	Yes	No
Pearce et al., 2008[39] Cardiovascular Risk Education and Social Support (CaRESS) Trial	Yes	No	NA	No	NA	NA	Yes	No
Powell et al., 1995[40] NA	Yes	No	No	No	NA	No	No	No
Powers et al., 2011[68] NA	Yes	No	No	No	NA	NA	Yes	No
Pyne et al., 2011[41] HIV Translating Initiatives for Depression Into Effective Solutions (HITIDES)	Yes	No	Yes	No	NA	NA	Yes	NA
Rich et al., 1996[42] NA	Yes	Yes	Yes	No	NA	No	Yes	No
Rickles et al., 2005[43] NA	Yes	No	No	No	NA	No	Yes	No
Ross et al., 2004[44] NR	Yes	Yes	Yes	No	NA	No	No	No
Rudd et al., 2004[45] NA	Yes	Yes	Yes	No	NA	No	Yes	No
Rudd et al., 2009[46] NA	Yes	No	No	No	NA	NA	Yes	No
Schaffer et al., 2004[47] NA	Yes	Yes	Yes	No	NA	No	Yes	No

Author, Year Trial Name	Relevant for KQ 1a?	Improvement in Medication Adherence?	Relevant for KQ 1b	Relevant for KQ 2a?	Improvement in Medication Adherence?	Relevant for KQ 2b	Relevant for KQ 3a?	Relevant for KQ 3b?
Schectman et al., 1994[48] NA	Yes	No	No	No	NA	No	Yes	No
Schneider et al., 2008[49] NA	Yes	Yes	Yes	No	NA	NA	Yes	No
Schnipper et al., 2006[50] NA	Yes	No	No	No	NA	No	Yes	No
Simon et al., 2006[51] NA	Yes	No	Yes	No	No	NA	Yes	No
Sledge et al., 2006[52] NA	Yes	No	No	No	NA	No	Yes	No
Smith et al., 2008[53] NR	Yes	Yes	No	No	NA	No	Yes	No
Solomon et al., 1998[54] NA Gourley et al., 1998[55] NA	Yes	Yes	Yes	No	NA	NA	Yes	No
Stacy et al., 2009[56] NA	Yes	Yes	No	No	NA	NA	Yes	No
Taylor et al., 2003[57] NA	Yes	No	No	no	NA	NA	Yes	no
Vivian et al., 2002[58] NA	Yes	No	No	No	NA	No	Yes	No
Waalen et al., 2009[59] NA	Yes	Yes	No	No	NA	No	Yes	No
Wakefield et al., 2011[60] NA	Yes	No	No	No	NA	NA	Yes	Yes
Weinberger et al., 2002[61] NA	Yes	No	No	No	NA	No	Yes	No
Weymiller et al., 2007[62] Statin Choice Randomized Trial Jones et al., 2009[63] Statin Choice Randomized Trial	Yes	No	No	No	NA	No	Yes	Yes, study comparison is of a single intervention characteristic (KQ3b results = KQ1/KQ2 results)

Author, Year Trial Name	Relevant for KQ 1a?	Improvement in Medication Adherence?	Relevant for KQ 1b	Relevant for KQ 2a?	Improvement in Medication Adherence?	Relevant for KQ 2b	Relevant for KQ 3a?	Relevant for KQ 3b?
Williams et al., 2010[64] NA	Yes	No	Yes	No	NA	NA	Yes	Yes, study comparison is of a single intervention characteristic (KQ3b results = KQ1/KQ2 results)
Wilson et al., 2010[65] Better Outcomes of Asthma Treatment (BOAT); note that there is online supplemental material for methods and timeline	Yes	Yes	Yes	No	NA	NA	Yes	Yes, study comparison is of a single intervention characteristic (KQ3b results = KQ1/KQ2 results)
Wolever et al., 2010[66] NA	Yes	Yes	Yes	No	NA	NA	No	NA
Zhang et al., 2010[67] NA	No	NA	NA	Yes	Yes	No	No	No

Table D7. Key Questions 4-5

Author, Year Trial Name	Any Medication Adherence Outcomes Reported for Subgroups (Relevant for KQ 4)?	List Relevant Subgroups	Study Entirely Conducted in a Vulnerable Subpopulation (Relevant for KQ 4)?	List Relevant Vulnerable Subpopulation	Relevant for KQ 5?
Bender et al., 2010[1] NA	No	NA	No	NA	No
Berg et al., 1997[2] NA	No	NA	No	NA	No
Berger et al., 2005[3] NA	No	NA	No	NA	No
Bogner et al., 2008[4] NA	Yes	Depression and diabetes co-morbidity	Yes	Depression and diabetes co-morbidity	No
Bogner et al., 2010[5] NA	Yes	Older African Americans	Yes	Older African American primary care patients	No
Bosworth et al., 2005[6] V-STITCH	No	NA	No	NA	No
Bosworth et al., 2008[7] TCYB Bosworth et al., 2007[8] TCYB Methods paper	No	NA	No	NA	No
Capoccia et al., 2004[9] NA	No	NA	No	NA	No
Carter et al., 2009[10] NA	No	NA	No	NA	Yes
Chernew et al., 2008[11] NA	No	NA	No	NA	No
Choudhry et al., 2010[12] NA	No	NA	No	NA	No
Choudhry et al., 2011[13] MI FREEE	No	NA	No	NA	No
Friedman et al., 1996[14] NA	No	NA	No	NA	No

Author, Year Trial Name	Any Medication Adherence Outcomes Reported for Subgroups (Relevant for KQ 4)?	List Relevant Subgroups	Study Entirely Conducted in a Vulnerable Subpopulation (Relevant for KQ 4)?	List Relevant Vulnerable Subpopulation	Relevant for KQ 5?
Fulmer et al., 1999[15] NA	Yes	Elderly	Yes	Elderly	No
Grant et al., 2003[16] NA	No	NA	No	NA	No
Guthrie et al., 2001[17] First Myocardial Infarction (MI) Risk Reduction Program	No	NA	No	NA	No
Hoffman et al., 2003[18] NA	No	NA	No	NA	No
Hunt et al., 2008[19] NA	No	NA	No	NA	No
Janson et al., 2003[20] NA	No	NA	No	nrNR	No
Janson et al., 2009[21] NA	No	NA	No	NA	No
Johnson et al., 2006[23] NR	No	NA	No	NA	No
Johnson et al., 2006[22] NR	No	NA	No	NA	No
Katon et al., 2001[28] NA Ludman et al., 2003[29] NA Van Korff et al., 2003[30] NA	No	NA	No	NA	No
Katon et al., 1995[24] NA	Yes	Major depression	No	NA	No
Katon et al., 1996[25] NA	Yes	Major depression	No	NA	No

Author, Year Trial Name	Any Medication Adherence Outcomes Reported for Subgroups (Relevant for KQ 4)?	List Relevant Subgroups	Study Entirely Conducted in a Vulnerable Subpopulation (Relevant for KQ 4)?	List Relevant Vulnerable Subpopulation	Relevant for KQ 5?
Katon et al., 1999[26] NA Katon et al., 2002[27] NA	Yes	Moderate- and high-severity depression	No	NA	No
Lee et al., 2006[31] FAME	Yes	Elderly ≥ 65 yrs old	Yes	Elderly ≥ 65 yrs old	No
Lin et al., 2006[32] NA	Yes	Depression and diabetes co-morbidity	Yes	Depression and diabetes co-morbidity	No
Maciejewski et al., 2010[33] NA	No	NA	No	NA	No
Mann et al., 2010[34] The Statin Choice	No	NA	No	NA	No
Montori et al., 2011[35]	No	NA	No	NA	No
Murray et al., 2007[36] NA	No	NA	No	NA	Yes
Nietert et al., 2009[37] NA	No	NA	No	NA	No
Okeke et al., 2009[38] NA	No	N-A	No	N-A	No
Pearce et al., 2008[39] Cardiovascular Risk Education and Social Support (CaRESS) Trial	No	NA	No	NA	No
Powell et al., 1995[40] NA	No	NA	No	NA	No
Powers et al., 2011[68] NA	No	NA	No	NA	No
Pyne et al., 2011[41] HIV Translating Initiatives for Depression Into Effective Solutions (HITIDES)	Yes	HIV comorbidity	Yes	HIV comorbidity	No
Rich et al., 1996[42] NA	Yes	Elderly (>= 70 years old)	Yes	Elderly (>= 70 years old)	No

Author, Year Trial Name	Any Medication Adherence Outcomes Reported for Subgroups (Relevant for KQ 4)?	List Relevant Subgroups	Study Entirely Conducted in a Vulnerable Subpopulation (Relevant for KQ 4)?	List Relevant Vulnerable Subpopulation	Relevant for KQ 5?
Rickles et al., 2005[43] NA	No	NA	No	NA	No
Ross et al., 2004[44] NR	No	NA	No	NA	No
Rudd et al., 2004[45] NA	No	NA	No	NA	No
Rudd et al., 2009[46] NA	No	NA	No	NA	No
Schaffer et al., 2004[47] NA	No	NA	No	NA	No
Schectman et al., 1994[48] NA	No	NA	No	NA	Yes
Schneider et al., 2008[49] NA	Yes	Elderly (≥65 years old)	Yes	Elderly (≥65 years old)	No
Schnipper et al., 2006[50] NA	No	NA	No	NA	No
Simon et al., 2006[51] NA	No	NA	No	NA	
Sledge et al., 2006[52#2608] NA	No	NA	No	NA	No
Smith et al., 2008[53] NR	No	NA	No	NA	No
Solomon et al., 1998[54] NA Gourley et al., 1998[55] NA	No	NA	No	NA	No
Stacy et al., 2009[56] NA	No	NA	No	NA	No
Taylor et al., 2003[57] NA	Yes	High risk patients in rural medically underserved area	Yes	High risk patients in rural medically underserved area	No
Vivian et al., 2002[58] NA	No	NA	No	NA	No

Author, Year Trial Name	Any Medication Adherence Outcomes Reported for Subgroups (Relevant for KQ 4)?	List Relevant Subgroups	Study Entirely Conducted in a Vulnerable Subpopulation (Relevant for KQ 4)?	List Relevant Vulnerable Subpopulation	Relevant for KQ 5?
Waalen et al., 2009[59] NA	No	N-A	No	N-A	No
Wakefield et al., 2011[60] NA	No	NA	No	NA	No
Weinberger et al., 2002[61] NA	No	NA	No	NA	No
Weymiller et al., 2007[62] Statin Choice Randomized Trial Jones et al., 2009[63] Statin Choice Randomized Trial	No	NA	No	NA	Yes
Williams et al., 2010[64] NA	No	NA	No	NA	No
Wilson et al., 2010[65] Better Outcomes of Asthma Treatment (BOAT); note that there is online supplemental material for methods and timeline	No	NA	No	Na	No
Wolever et al., 2010[66] NA	No	NA	No	NA	No
Zhang et al., 2010[67] NA	Yes	Elderly (age ≥65 years)	Yes	Elderly (age ≥65 years)	No

Table D8. Participant baseline characteristics

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Bender et al., 2010[1] NA	Overall N: NR G1: 39.6 (12.8) G2: 43.5 (14.3)	Overall N: NR G1: 60% G2: 68%	**White** G1: 56% G2: 60% **Hispanic** G1: 24% G2: 12% **African American** G1: 20% G2: 20% **Asian** G1: 0% G2: 8%	No	NA	**Other (Theory)**: Benefit-risk model of health behavior.
Berg et al., 1997[2] NA	Overall N: 55 G1: 47 (15) G2: 52 (15)	Overall N: 55 G1: 21 (68%) G2: 15 (62%)	Overall N: 55 **Caucasian** G1: 29 (93%) G2: 23 (96%) **non-Caucasian** G1: 2 (7%) G2: 1 (4%)	Yes	**Income** Overall N: 55 <10K G1: 20% G2: 12% 10-30K G1: 43% G2: 29% 30-50% G1: 17% G2: 25% **Insurance (yes)** G1: 93% G2: 87% **Health problems** G1: 48% G2: 54%	

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Berg et al., 1997[2] NA (continued)					**Asthma severity moderate** G1: 71% G2: 79% severe G1: 29% G2: 21% **Health Problems** (yes) G1: 48% G2: 54% **Chronolog compliance mean** (SD) G1: 43 (29) G2: 40 (26) No sig diff	
Berger et al., 2005[3] NA	Overall N: 367 Overall age: 45.98 (9.13) G1: NR G2: NR	Overall N: 367 Overall % female: 82.8 G1: NR G2: NR	Overall N: NR G1: NR G2: NR	No	NR	
Bogner et al., 2008[4] NA	Overall N: 64 G1: 59.7 (7.3) G2: 57.5 (6.3)	Overall N: G1: 24 (75.0) G2: 25 (78.1)	African American, n (%) G1: 25 (78.1) G2: 28 (87.5)	Yes	**SF-36 scores:** **Physical function score, mean (SD)** G1: 54.1 (33.2) G2: 64.5 (34.9) p= .22 **Social function score, mean (SD)** G1: 75.6 (37.6) G2: 83.8 (33.5) p=.37	**Funding** multiple sources: American Heart Association Grant-in-Aid, and an NIMH Mentored Patient-Oriented Research Career Development Award **Theory**: Integrated Care Model

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Bogner et al., 2008[4] NA (continued)					**Role physical score, mean (SD)** G1: 55.5 (42.0) G2: 65.6 (42.5) p= .34 **Role emotional score, mean (SD)** G1: 63.5 (46.7) G2: 74.0 (43.0) p= .36 **Bodily pain score, mean (SD)** G1: 46.3 (33.1) G2: 60.6 (35.7) p= .10 **<u>Other covariates</u>** **MMSE, mean (SD)** G1: 27.7 (2.7) G2: 27.9 (3.2) p= .73 **Number of medications, N (SD)** G1: 8.6 (5.1) G2: 7.0 (3.6) p= .16 **<u>Outcome measures</u>** **CES-D, mean (SD)** G1: 17.5 (13.2) G2: 19.6 (14.2) p=.54	

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Bogner et al., 2008[4] NA (continued)					**Systolic BP, mean (SD), mm Hg** G1: 146.7 (20.9) G2: 143.1 (22.5) p= .51 **Diastolic BP, mean (SD), mm Hg** G1: 83.0 (10.7) G2: 81.4 (11.1) p=.58 **≥80% adherent to antidepressant, N (%)** G1: 14 (43.0) G2: 16 (50.0) p= .81 **≥80% adherent to antihypertensive, N (%)** G1: 16 (50.0) G2: 11 (34.4) p= .31	

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Bogner et al., 2010[5] NA	Overall N: Mean (SD) = 60.2 (7.4) G1: 61.6 (8.3) G2: 58.3 (6.3)	Overall N: 84.5% G1: 82.8% G2: 86.2%	**Black** Overall N: 100% G1: 100% G2: 100%	Yes	**Less than high school education** Overall N: 13 G1: 8 (27.6%) G2: 5 (17.2%) **Lives alone** Overall N: 27 G1: 16 (55.2%) G2: 11 (37.9%) **Role Physical Score** Overall N: NR G1: 44.0 (39.9) G2: 64.5 (42.5) **Number of Medications** Overall N: NR G1: 10.2 (3.3) G2: 7.7 (3.2) **Adherent at baseline oral hypoglycemics** Overall N: NR G1: 34.5% G2: 20.7% **Adherent at baseline anti-depressants** Overall N: NR G1: 27.6% G2: 13.8%	**Funding source** Non-profit (American Diabetes Association) and Academic (University of Pennsylvania's Institute on Aging) **Theoretical model** Conceptual framework adapted from Cooper et al (source 33)

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Bosworth et al., 2005[6] V-STITCH	Overall N: NR G1: 63 (11.24) G2: 64 (11.48)	Overall N: NR G1: 2% G2: 2%	**White** Overall N: NR G1: 56 G2: 58 **African-American** Overall N: NR G1: 41 G2: 39	Yes	**High school or less, %** Overall N: NR G1: 50 G2: 51 **Inadequate income, %** Overall N: NR G1: 23 G2: 21 **Diabetic, %** Overall N: NR G1: 38 G2: 42 **Adherent to medications (based on self-report), %** Overall N: 66 G1: NR G2: NR	**Additional theoretical model**: Health Decision **Theoretical Model** HDM

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Bosworth et al., 2008[7] TCYB Bosworth et al., 2007[8] TCYB Methods paper	Overall N: NR G1: 61 (12.7) G2: 62 (11.9)	Overall N: NR G1: 65 G2: 67	**Caucasian, %** Overall N: NR G1: 50% G2: 47% **African American, %** Overall N: NR G1: 47% G2: 51%	Yes	**12th grade or less** Overall N: NR G1: 35% G2: 38% **Functionally illiterate (REALM<=60), %** Overall N: NR G1: 27% G2: 27% **Inadequate income, %** Overall N: NR G1: 18% G2: 21% **Diabetic, %** Overall N: NR G1: 34% G2: 38%	**Funding source:** NHLBI, Pfizer Health Literacy Communication Initiative grant, American Heart Association Established-Investigator award **Theoretical model:** also Health Decision Model and motivational interviewing

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Capoccia et al., 2004[9] NA	Overall N: 74 G1: 38.2 ± 13.8 G2: 39.4 ± 13.4 p=0.71	Overall N: 57 (77) G1: 34 (83) G2: 23 (70) p=0.18	**Non-White** Overall N: 16 (22) G1: 9 (22) G2: 7 (21) p=0.94	Yes	**Annual household income <$30,000** Overall N: 19 (26) G1: 12 (29) G2: 7 (21) p=0.36 **Panic disorder** G1: 9 (22) G2: 5 (15) p= 0.43 **Neuroticism score** (Mean ± S.D. NEO) G1: 12.4 ± 6.1 G2: 11.0 ± 5.5 p= 0.31 **Dysthymic disorder** G1: 23 (56) G2: 16 (48) p= 0.40 **Prior antidepressant for depression** G1: 20 (49) G2: 12 (36) p= 0.28 **Prior counseling or psychotherapy** G1: 17 (41) G2: 17 (52) p= 0.39	

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Capoccia et al., 2004[9] NA (continued)					**Mean ± S.D. SCL-20 score** **No. (%) with SCID major depression** G1: 21 (53) G2: 9 (28) p= 0.04 **Mean ± S.D. SF-12 Index (physical) score** G1: 49.6 ± 1.6 G2: 52.6 ± 1.6 p= 0.68 **Mean ± S.D. SF-12 Index (mental) score** G1: 28.0 ± 1.6 G2: 29.0 ± 1.7 p= 0.20	
Carter et al., 2009[10] NA	Overall N: NR G1: 57.3 (14.3) G2: 59.2 (13.8)	Overall N: NR G1: 62.5% G2: 55.7%	**White/Caucasian** Overall N: NR G1: 85.9% G2: 77.6% **African-American** Overall N: NR G1: 6.8% G2: 19.5% **American Indian** Overall N: NR G1: 0.5% G2: 1.0% **>1 Race or Other** Overall N: NR G1: 2.6% G2: 1.9%	Yes	**Low self-reported medication adherence (i.e., score ≥3) (%)** Overall N: NR G1: 8.9% G2: 9.1% NS **Household income <$25,000 (%)** Overall N: NR G1: 21.4% G2: 51.9% p < 0.001	

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Carter et al., 2009[10] NA (continued					**Insurance status (%):** Individual/group plan G1: 56.3% G2: 32.4% Medicare/Medicaid G1: 37.0% G2: 40.5% Self-pay or other G1: 6.8% G2: 27.1% p < 0.001 **Married** Overall N: NR G1: 67.7%% G2: 43.3% p: <0.001 **BMI (kg/m^2) (Mean (SD))** Overall N: NR G1: 32.1 (6.8) G2: 34.2 (8.7) p: 0.010 **Diabetes mellitus (%)** Overall N: NR G1: 19.8% G2: 38.1% p < 0.001 **Heart failure (%)** Overall N: NR G1: 0.5% G2: 1.9% NS	

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Carter et al., 2009[10] NA (continued					**Chronic kidney disease (%)** Overall N: NR G1: 5.7% G2: 7.6% NS **Angina (%)** Overall N: NR G1: 0.5% G2: 5.7% p < 0.003 **Peripheral arterial disease (%)** Overall N: NR G1: 2.1% G2: 1.9% NS **Left ventricular hypertrophy (%)** Overall N: NR G1: 1.6% G2: 1.4% NS **≥1 Coexisting condition (%)** Overall N: NR G1: 90.1% G2: 95.2% p=0.051 **No. of coexisting conditions (Mean (SD))** Overall N: NR G1: 2.8 (1.8) G2: 3.6 (2.2) p < 0.001	

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Chernew et al., 2008[11] NA	Overall N (2004): G1: 37.4 G2: 43.9 Overall N (2005): G1: 38.0 G2: 44.7	Overall N (2004): G1: 53.5 G2: 51.2 Overall N (2005): G1: 53.5 G2: 51.2	NR	No	NA	"**Other" Theoretical Model** = None specified **"Other" Level of Randomization** = Not applicable
Choudhry et al., 2010[12] NA	Total sample Overall N: NR G1: 58.8 (NR) G2: 67.5 (NR) G3: 53.8 (NR) G4: 54.5 (NR) G1 and G3: p<0.05 G2 and G4 p<0.05	Total sample Overall N: NR G1:36.1% G2: 37.6% G3: 39.8% G4: 28.8% G1 and G3: p<0.05 G2 and G4 p<0.05	**Black** Total sample Overall N: NR G1: 11.5% G2:10.2% G3: 11.9% G4: *12.3%* *G2 and G4 p<0.05*	Yes	**Income (Mean):** Overall: NR G1: $56,625 G2: $54,715 G3: $58,263 G4: $57,286 **Coronary artery disease (%):** Overall N: NR G1: 26.3% G2: 60.6% G3: 25.3% G4:43.8% **Congestive heart failure:** Total sample: Data NR **Statin users** Overall N: NR G1: 1.8% G2: 1.8% G3: 1.8% G4: 2.4% **Hypertension:** Overall: NR G1: 50.0% G2: 55.5% G3: 59.5% G4: 46.4%	Study design - Other = Interrupted time series with concurrent control group Level of randomization - Other = NA Theoretical model - Other = Value-based insurance design strategy

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Choudhry et al., 2010[12] NA (continued)					**Diabetes**: Overall: NR G1: 36.2% G2: 12.6% G3 34.5% G4: 9.9% **Charlson comorbidity score:** Overall: NR G1: 1.0 G2: 3.3 G3: 1.0 G4: 3.3 **Monthly drug copay (year before copay reduction):** Overall: NR G1: $24.18 G2: $17.22 G3: $11.80 G4: 10.65 G1 and G3 differ on income, hypertension and copay at $p < 0.05$ G2 and G4 differ income, CAD, Hypertension, diabetes and copay at $p < 0.05$	

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Choudhry et al., 2011[13]	Overall N: 5855 G1: 53.6 (7.6) G2: 53.7 (7.6)	Overall N: 5855 G1: 24.4 G2: 25.3	Overall N: NR G1: NR G2: NR	Yes	**Congestive heart failure** Overall N: 5855 G1: 27.0 G2: 29.1 **COPD** Overall N: 5855 G1: 15.7 G2: 16.4 **Diabetes** Overall N: 5855 G1: 34.3 G2: 34.8 **Hypertension** Overall N: 5855 G1: 71.2 G2: 72.4 **Previous MI** Overall N: 5855 G1: 15.6 G2: 17.4 **Stroke** Overall N: 5855 G1: 5.8 G2: 6.7	NA
Friedman et al., 1996[14] NA	Overall N: 76 G1: 76 G2: 77	Overall N: 77 G1: 75 G2: 79	**Black %** Overall N: 11% G1: 10% G2: 11%	Yes	**Education (%):**Overall N: NR 1-11 G1: 20 G2: 32 12 G1: 55 G2: 51	**"Other" theoretical model** = none specified

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Friedman et al., 1996[14] NA (continued)					13-17 G1: 25 G2: 17 **Employed (%)** G1: 9 G2: 10 **Comorbid disease** (%) Heart disease G1: 29 G2: 34 Stroke G1: 6 G2: 7 Diabetes G1: 20 G2: 16 Other G1: 80 G2: 82 **Mean number of comorbid disease** G1: 1.2 G2: 1.2 **Mean medication adherence** G1: 93 G2: 94 **Mean systolic BP (mm Hg)** G1: 169.5 G2: 167	
Friedman et al., 1996[14] NA (continued)					**Mean diastolic BP (mm Hg)** G1: 86.1 G2: 84.0	

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Fulmer et al., 1999[15] NA	Overall N: 50 G1: 73.1 (6.5) G2: 76.2 (8.8) G3: 73.7 (5.3)	Overall N: NR G1: G2:	Overall N: 50 **White** G1: 23.5 G2: 20.0 G3: 0.0 **Black** G1: 23.5 G2: 33.3 G3: 33.3 **Other** G1: 50.0 G2: 46.7 G3: 61.1	yes	**Average compliance rates at BL** G1: 82% G2: 76% G3: 81%	**Funding Source:** Pharma, private foundation **Theoretical Model:** Article describes using a "stimulant strategy"

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Grant et al., 2003[16] NA	Overall N: (for all randomized to G1 and G2) NR G1: 63.3 (12.7) G2: 64.9 (12.1) Overall N: for completers (NR) G1: 64 (12) G2: 69 (10)	Overall (all randomized to G1 and G2) N: NR G1: 52 G2: 51 Overall N (all completers): NR G1: 55 G2: 69	Overall N randomized: NR G1: % white: 79 G2: % white: 89 Overall N for completers: NR G1: % white: 87 G2: % white: 93	Yes	**Baseline Medication Adherence (# days adherent in last 7 days)** Overall N for completers: NR G1: 6.7 (0.9) G2: 6.9 (0.4) **HbA1c (mean (SD))** Overall (all randomized to G1 or G2: NR G1: 7.7 (1.6) G2: 7.6 (1.4) Overall N (completers): NR G1: 7.7 (1.7) G2: 7.5 (1.1) **Number of Medicines (mean (SD))** Overall N (Completers): NR G1: 6 (2.8) G2: 5.8 (2.7)	**Other Theoretical Model** = None

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Guthrie et al., 2001[17] First Myocardial Infarction (MI) Risk Reduction Program	Overall N: 58.0 (NR) G1: 57.9 (NR) G2: 58.3 (NR)	Overall N: 51.1 G1: 50.8 G2: 52.4	**White** Overall N: 79.9 G1: 80.0 G2: 79.6 **Black** Overall N: 9.0 G1: 9.0 G2: 9.2 **Hispanic** Overall N: 6.4 G1: 6.4 G2: 6.4 **Asian** Overall N: 1.8 G1: 1.7 G2: 2.2	Yes	**Prescription health plan, %** Overall N: 77.4 G1: 77.5 G2: 77.2 **Level of education-elementary, %** Overall N: 9.8 G1: 9.8 G2: 9.4 **Level of education-high school, %** Overall N: 53.8 G1: 53.9 G2: 53.4 **Level of education-college, %** Overall N: 25.9 G1: 25.8 G2: 26.2 **Level of education-graduate or professional, %** Overall N: 10.6 G1: 10.5 G2: 10.9	**Theoretical model**: not specified **<$15,000, %** Overall N: 20.6 G1: 21.0 G2: 19.0 **$15,001-$25,000, %** Overall N: 21.2 G1: 21.2 G2: 21.4 **$25,001-$50,000, %** Overall N: 31.0 G1: 31.1 G2: 30.8 **$50,001-$100,000, %** Overall N: 21.7 G1: 21.1 G2: 23.7 **>$100,000, %** Overall N: 5.5 G1: 5.6 G2: 5.1 **Diabetic (male), %** Overall N: 8.8 G1: 8.1 G2: 8.9 **Diabetic (female), %** Overall N:9.8 G1: 9.6 G2: 9.8

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Hoffman et al., 2003[18] NA	Overall N: NR G1: 51.9 (16.7) G2: 51.2 (16.5)	Overall N: 68 G1: 67.9 G2: 67.6	NR	No	NA	**Other (Level of randomization):** random selection of zip codes of physicians' offices for inclusion in study. Allocation conducted by listing zip codes numerically and alternating arms. **Multiple funding sources:** Pharma companies & insurance provider **Theoretical Model:** No theoretical model reported
Hunt et al., 2008[19] NA	Overall N: NR G1: 68 (12) G2: 68 (13)	Overall N: NR G1: 63 G2: 66	NR	Yes	**Comorbidities, N (%):** Overall N: NR **G1:** Asthma or COPD, 27 (12) Diabetes, 59 (26) History of stroke, 15 (7) Coronary artery disease, 46 (20) Renal impairment, 8 (3) One or more chronic conditions, 111 (48) Baseline systolic BP (mean (SD)), 173 (15) Baseline diastolic BP (mean (SD)), 90 (14)	

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Hunt et al., 2008[19] NA (continued)					**G2**: Asthma or COPD, 27 (12) Diabetes, 57 (25) History of stroke, 6 (3) Coronary artery disease, 43 (18) Renal impairment, 6 (3) One or more chronic conditions, 103 (44) Baseline systolic BP (mean (SD)), 174 (15) Baseline diastolic BP (mean (SD)), 92 (14) **Education, college, N (%)** G1: 64 (28) G2: 65 (28) Only statistical sig between group difference was history of stroke, p=0.04	
Janson et al., 2003[20] NA	Overall N: 65 G1: 32 (9) G2: 35 (8)	Overall N: G1: 18 (55%) G2: 18 (56%)	NR	Yes	No group differences at baseline: **BL values: Adherence to inhaled corticosteroid (%)** G1: 70 (30) G2: 65 (34)	col X: no explicit theory used but testing whether imparting basic information and skills will lead to behavior that will improve asthma control

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Janson et al., 2003[20] NA (continued)					**Quality of life*** G1:27 (13) G2: 24 (14) **Perceived control of asthma** G1: 37 (6) G2: 42 (5) **Symptom severity** G1:11 (6) G2: 7 (6) **Beta-agonist (puffs)** G1: 4 (3) G2: 3 (3) **FEV1 (% predicted)** G1: 83 (17) G2: 80 (20) **Morning peak flow (L/min)** G1: 446 (125) G2: 363 (97) **Eosinophil cationic protein** G1: 319 +/- 277 G2: 324 (346) **Tryptase (g/L)** G1: 10 (22) G2: 3 (5) **Eosinophil's (%)** G1: 6 (8) G2: 7 (12)	

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Janson et al., 2003[20] NA (continued)					**Neutrophils (%)** G1: 39 (17) G2: 44 (19)	
Janson et al., 2009[21] NA	Overall N: 84 G1: 36.8 +/- 9.4 G2: 39.7 +/- 9.3	Overall N: G1: 24 (53) G2: 21 (54)	**Asian** G1: 10 (22) G2: 6 (15) **Black** G1: 1 (2) G2: 4 (10) **White** G1: 28 (62) G2: 26 (67) **Other** G1: 6 (14) G2: 3 (8)	Yes	**Insured:** Overall N: G1: 37 (82) G2: 27 (69) **Severity by FEV1 criteria:** Severe (60% predicted value) G1: 22 (49) G2: 18 (46); **Adherence to ICS (%)** G1: 82 +/- 18 G2: 81 +/- 18, p=.71 only statistically sign difference across groups: peak flow **Peak flow (morning only)** G1: 427.4 +/- 91.1 G2: 381.8 +/- 110.2 , p=0.04 **Other markers of severity**: Perceived asthma control score (11-55) G1: 41.8 +/- 6.1 G2: 40.2 +/- 4.2, p=.14	**Funding sources** - gov't and pharma

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Janson et al., 2009[21] NA (continued)					**Asthma quality-of-life score (0-80)** G1: 16.0 +/- 11.0 G2: 15.8 +/- 11.1, p=.94 **Peak flow (morning only)** G1: 427.4 +/- 91.1 G2: 381.8 +/- 110.2, p=.04 **Mean weekly puffs of b-agonist used** G1: 1.5 +/- 1.9 G2: 1.7 +/- 2.2, p= .71 **Mean weekly symptom score** G1: 4.5 +/- 4.4 G2: 5.1 +/- 5.1, p=.55 **Mean % symptom-free days per week** G1: 34.1 +/- 37.1 G2: 31.0 +/- 37.2, p=.70 **Mean weekly number of nighttime awakenings** G1: 0.29 +/- 0.69 G2: 0.35+/- 0.97, p=.75	

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Johnson et al., 2006[22] NR	Overall N: NR G1: NR G2: NR	Overall N: 49.6 G1: NR G2: NR	**White** Overall N: 83.0 G1: NR G2: NR **Black** Overall N: 5.8 G1: NR G2: NR **Other** Overall N: 11.2 G1: NR G2: NR	Yes	**Under $25,000, %** Overall N: 21.8 G1: NR G2: NR **$25,000-$50,000, %** Overall N: 33.1 G1: NR G2: NR **$50,000-$75,000, %** Overall N: 21.8 G1: NR G2: NR **$75,000 or above, %** Overall N: 23.4 G1: NR G2: NR	
Johnson et al., 2006[23] NR	Overall N: 55.7 (median) G1: NR G2: NR	Overall N: 47.0 G1: NR G2: NR	**White** Overall N: 76.4 G1: NR G2: NR **Black** Overall N: 16.1 G1: NR G2: NR **Other** Overall N: 7.5 G1: NR G2: NR	Yes	**Under $25,000, %** Overall N: 15.9 G1: NR G2: NR **$25,000-$50,000, %** Overall N: 29.1 G1: NR G2: NR **$50,000-$75,000, %** Overall N: 22.1 G1: NR G2: NR **$75,000 or above, %** Overall N: 32.9 G1: NR G2: NR	none

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Katon et al., 1995[24] NA	Overall N: 217 Major depression group N=91 G1: 43.2 (15.4) G2: 42.3 (12.7) Minor depression group N=126 G1: 52.2 (14.3) G2: 50.3 (15.1)	Overall N: 217 Major depression group N=91 G1: 77.5 G2: 88.1 Minor depression group N=126 G1: 76.3 G2: 68.7	NR	yes	Overall N: 217 **SCL mean (SD) depression score** Major depression group N=91 G1: 2.35 (0.49) G2: 2.23 (0.48) Minor depression group N=126 G1: 1.67 (0.40) G2: 1.72 (0.56) **IDS mean (SD) score** Major depression group N=91 G1: 46.6 (9.0) G2: 45.1 (11.2) Minor depression group N=126 G1: 29.1 (9.6) G2: 28.0 (9.5) **Chronic disease score mean (SD) score** Major depression group N=91 G1: 1.3 (1.9) G2: 0.6 (1.4) Minor depression group N=126 G1: 2.3 (3.2) G2: 1.5 (1.9)	**Other Theoretical Model**: unspecified

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Katon et al., 1996[25] NA	Overall N: NR Major Depression Group G1: 43.1 (9.3) G2: 44.8 (15.9) Minor Depression Group G1: 49.2 (13.9) G2: 47.2 (13.8)	Overall N: NR Major Depression Group G1: 77.4 G2: 73.5 Minor Depression Group G1: 71.7 G2: 73.8	Overall N: NR Major Depression Group (% White) G1: 77.4 G2: 91.2 Minor Depression Group (% White) G1: 91.3 G2: 85.7	Yes	**≥1 year of college (%)** Major Depression Group G1: 90.3 G2: 70.6 Minor Depression Group G1: 87.0 G2: 81.0 **Chronic disease (mean (SD)):** Overall N: NR Major Depression Group G1: 1.19 (1.6) G2: 1.1 (2.0) Minor Depression Group G1: 1.5 (2.6) G2: 1.2 (2.3) **Inventory of Depressive Symptoms Score (mean (SD))** Major Depression Group G1: 46.8 (10.8) G2: 46.0 (8.8) Minor Depression Group G1: 27.3 (7.4) G2: 28.2 (11.3)	Column X: "Other" Theoretical Model = Social Cognitive theory and Social Learning theory

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Katon et al., 1996[25] NA (continued)					**SCL-20 (mean (SD))** Major Depression Group G1: 2.46 (0.53) G2: 2.35 (0.51) Minor Depression Group G1: 1.77 (0.49) G2: 1.62 (0.54) **Recurrent major depression (≥2 episodes)** Major Depression Group G1: 59.1 G2: 65.4 Minor Depression Group G1: 66.7 G2: 64.9	

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Katon et al., 2001[28] NA Ludman et al., 2003[29] NA Van Korff et al., 2003[30] NA	Overall N: 387 (reported as 386 in Ludman et al. and Katon et al.) G1: 46.4 (11.9) G2: 45.6 (13.3)	Overall N: 387 (reported as 386 in Ludman et al. and Katon et al.) G1: 75.4 G2: 71.9	Overall N: 387 (reported as 386 in Ludman et al. and Katon et al.) **% Caucasian**: G1: 92.3 G2: 88.0	Yes	**Severity of Depression** **% with major depression within past 2 years** Overall N: 387 (reported as 386 in Ludman et al. and Katon et al.) G1: 78.5 G2: 87.5 p=0.01 **SCL Depression Score (range 0 to 4), mean (SD)** G1: 0.83 (0.39) G2. 0.84 (0.35) **Comorbidity: Chronic Disease Score, mean (SD)** G1: 1051.4 (1228.0) G2: 1009.2 (994.5)	NA

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Katon et al., 1999[26] NA Katon et al., 2002[27] NA	Overall N: NR G1: 47.2 (14) G2: 46.7 (13.4)	Overall N: NR G1: 67.5 G2: 81.6 p= 0.02	**% Caucasian** Overall N: NR G1: 79.8 G2: 80.7	Yes	**Severity of Depression SCL Depression score** G1: 1.9 (0.5) G2: 1.9 (0.5) **Moderate depression:** N=149 **Severe depression**: N=79 **Recurrent depression (>= 3 episodes), %** G1: 76.3 G2: 83.3 **Dysthymia, %** G1: 40.0 G2: 59.8 **Chronic disease score; mean (SD)** G1: 1191.3 (978.5) G2: 1368.3 (1292.9)	**Other Randomization**;: Patients stratified by severity of disease (moderate or high) prior to randomization. **Other Theoretical Model**: NR

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Lee et al., 2006[31] FAME	*Overall N: 78 (8.3) G1: 77 (10.5) G2: 78 (6.2)	*Overall N: 22.9 G1: 25.3 G2: 26.3	**White** Overall N: 63.7 G1: 61.4 G2: 56.5 **Black** Overall N: 32.3 G1: 34.9 G2: 40.8	Yes	**<High School, %** *Overall N: 7.5 G1: 3.7 G2: 12.9 **High School graduate, %** *Overall N: 33.8 G1: 32.1 G2: 38.6 **College graduate, %** *Overall N: 21.4 G1: 24.7 G2: 18.6 **Drug-treated hypertension, %** *Overall N: 91.5 G1: 92.8 G2: 90.8 **Drug-treated hyperlipidemia, %** *Overall N: 80.6 G1: 83.1 G2: 80.3 **BL adherence at completion of run-in phase, mean (SD)** Overall N: 61.2 (13.5) G1: 61.4 (13.0) G2: 61.1 (14.1)	**Other Theoretical Model =** not specified *Overall N for baseline characteristics reported for beginning of run-in phase

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Lin et al., 2006[32] NA	Overall N: Mean (SD) = 58.5 (NR) G1: Mean (SD) = 58.6 (11.8) G2: Mean (SD) = 58.1 (12.0)	Overall N: 66.6% G1: 65.2% G2: 64.8%	**White** Overall N: 80% G1: 81.1% G2: 75.2% No other race/ethnicity data provided	Yes	**Type 2 Diabetes** Overall N: NR G1: 96.3% G2: 95.8% **Number of Diabetic Complications** G1: Mean (SD) = 1.5 (1.4) G2: Mean (SD) = 1.5 (1.3) **Major Depression (co-morbidity)** Overall N: NR G1: 62.6%% G2: 69.1% **≥3 Previous Episodes of Depression (co-morbidity)** Overall N: NR G1: 68.6% G2: 60.5% **BL SCL-20 Score (Depression severity)** Overall N: NR G1: Mean (SD) = 1.7 (0.5) G2: Mean (SD) = 1.6 (0.5)	**Other Theoretical model** = Intervention design and procedures based on the Pathways Study (source 24)

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Maciejewski et al., 2010[33] NA	**Diuretics** Overall N: NR G1: 51.7 (7.9) G2: 52.0 (7.8) **ACE Inhibitors** Overall N: NR G1: 51.8 (8.0) G2: 52.2 (7.9) **Statins** Overall N: NR G1: 53.0 (7.3) G2: 53.4 (7.2) **Beta Blockers** Overall N: NR G1: 52.0 (8.2) G2: 52.4 (8.0) **Calcium Channel Blockers** Overall N: NR G1: 52.6 (7.8) G2: 52.8 (7.7) **Metformin** Overall N: NR G1: 51.6 (8.4) G2: 51.7 (8.3) **ARBS** Overall N: NR G1: 52.3 (7.6) G2: 52.6 (7.5)	**Diuretics** Overall N: NR G1: 55% G2: 63% **ACE Inhibitors** Overall N: NR G1: 38% G2: 45% **Statins** Overall N: NR G1: 38% G2: 46% **Beta Blockers** Overall N: NR G1: 46% G2: 54% **Calcium Channel Blockers** Overall N: NR G1: 40% G2: 48% **Metformin** Overall N: NR G1: 45% G2: 54% ARBS Overall N: NR G1: 45% G2: 54%	Overall N: NR G1: NR G2: NR	Yes	Comorbidity burden (mean, SD) **Diuretics** Overall N: NR G1: 2.51 (2.59) G2: 2.51 (2.59) **ACE Inhibitors** Overall N: NR G1: 2.82 (3.01) G2: 2.85 (3.02) **Statins** Overall N: NR G1: 2.95 (3.03) G2: 2.95 (3.11) **Beta Blockers** Overall N: NR G1: 3.51 (3.53) G2: 3.59 (3.72) **Calcium Channel Blockers** Overall N: NR G1: 2.98 (3.24) G2: 3.09 (3.37) **Metformin** Overall N: NR G1: 2.87 (2.54) G2: 2.88 (2.60) **ARBS** Overall N: NR G1: 2.90 (3.01) G2: 2.91 (3.11)	NA

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Maciejewski et al., 2010[33] NA (continued)	**Cholesterol Absorption Inhibitors** Overall N: NR G1: 53.5 (7.1) G2: 53.8 (7.0)	**Cholesterol Absorption Inhibitors** Overall N: NR G1: 37% G2: 44%			**Cholesterol Absorption Inhibitors** Overall N: NR G1: 3.35 (3.19) G2: 3.40 (3.38)	
Mann et al., 2010[34] The Statin Choice	Overall N: 58 (11.5) G1: 58 (12) G2: 58 (11)	Overall N: Text states 58%, but the numbers in the table are not consistent with that G1: 74% G2: 75%	Overall N: Black or Latino: 89% G1: Black or Latino: NR G2: Black or Latino: NR	Yes	**< HS Education** Overall N: 44% G1: 51% G2: 36% **Mean HBA1c** Overall N: mean 7.5 (SD 2.0) G1: 7.0 (6.4, 8.7) (median (IQR)) G2: 6.7 (6.3, 7.6) (mean (IQR)) **10 year Cardiovascular Risk (%)** Overall N: < 15% risk: 53% 15-30% Risk: 44% > 30% Risk: 3% G1: < 15% risk: 53% 15-30% Risk: 40% > 30% Risk: 5% G2: < 15% risk: 54% 15-30% Risk: 41% > 30% Risk: 3% **BL Statin Use** Overall N: 69% G1: 69% G2: 69%	

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Motori et al., 2011[35]	Overall N: NR G1: median 67 (range 51-84) G2: median 67 (range 50-82)	Overall N: 100 G1: 100 G2: 100	Overall N: NR G1: NR G2: NR	Yes	**Annual income** Overall N: NR G1: Median 50000 (range 25000-90000) G2: Median 35000 (range 25000-70000)	NA
Murray et al., 2007[36] NA	Overall N: NR G1: 61.4 (SD 7.7) G2: 62.6 (SD 8.8)	Overall N: NR G1: 68.0% G2: 66.1%	Overall N: NR G1: Black 45.1%, White 54.1%, Other 0.8% G2: Black 52.1%, White 46.9%, Other 1.0%	Yes	**Sufficient income** G1: 62% G2: 64% **Mean education** G1: 11 (SD 2) G2: 11 (SD 3) **Health literate** G1: 72% G2: 71% **Medicare** G1: 54.1% G2: 56.3% **Medicaid** G1: 30.3% G2: 36.5%	

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Nietert et al., 2009[37] NA	Overall N: 60 (16) G1: 59.9 (16.7) G2: 60.6 (16.0) G3: 59.7 (16.5)	Overall N: NR G1: NR G2: NR	**Black** Overall N: NR G1: 16.3% G2: 16.3% G3: 16.5%	Yes	**Income (Mean (SD))** Overall N: NR G1: $33,573 ($9029) G2: $33751 ($9339) G3: $33471 ($9448) **Insurance Status** Medicaid G1: 16.4% G2: 13.2% G3: 15.7% Other G1: 72.8% G2: 76.2% G3: 73.1% None G1: 10.8% G2: 10.6% G3: 11.2% **Disease indication Diabetes** G1: 12.2% G2: 12.2% G3: 10.5% **Hypertension or heart failure** G1: 56.8% G2: 55.9% G3: 56.0% **Hyperlipidemia** G1: 17.2% G2: 16.9% G3: 17.7%	**Theoretical model - Other** = NS

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Nietert et al., 2009[37] NA (continued)					**Depression** G1: 13.2% G2: 14.6% G3: 15.1% **Psychosis** G1: 1.4% G2: 1.2% G3: 1.2%	
Okeke et al., 2009[38] NA	Overall N: NR G1: 66.2 (13.1) G2: 63.8 (13.4)	Overall N: NR G1: 48.6 G2: 41.9	**Black:** Overall N: NR G1: 65.7 G2: 54.8 **White**: Overall N: NR G1: 34.3 G2: 41.9 **Asian**: Overall N: NR G1: 0.00 G2: 3.23	Yes	**Family income based on zip code**: Overall N: NR G1: ≤35K: 34.4%; 35-50K: 22.9%; 57-75K: 11.4%; >75K: 31.4%; unknown: 0% G2: ≤35K: 25.8%; 35-50K: 16.1%; 50-75K: 38.7%; >75K: 16.1%; unknown: 3.23% **Depression score mean (SD):** Overall N: NR G1: 0.47 (0.46) G2: 0.42 (0.54) **BL adherence:** Overall N: NR G1: 54% G2: 46%	Column Q: NIH, Pharma company (Alcon), grant from the Paul & Evanina Bell Mackall Foundation Trust, and the Wilmer Institute Research Program.

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Pearce et al., 2008[39] Cardiovascular Risk Education and Social Support (CaRESS) Trial	Overall N: Mean (SD) = 62.1 (10.79) G1: Mean (SD) = 60.3 (9.44) G2: Mean (SD) = 62.0 (11.51) G3: Mean (SD) = 63.1 (10.98)	Overall N: 55.3% G1: 48.0% G2: 65.5%	**White** Overall N: 86.9% G1: 88.0% G2: 82.8% **African-American** Overall N: 13.1% G1: 12.0% G2: 17.2%	Yes	**Health insurance (%)** Group/private: Overall N: 60.9% G1: 53.1% G2: 51.9% G3: 70.3% Medicaid/Medicare: Overall N: 32.8% G1: 32.7% G2: 42.3% G3: 27.5% Other: Overall N: 1.0% G1: 0.0% G2: 3.7% G3: 0.0% None: Overall N: 5.2% G1: 14.3% G2: 1.9% G3: 2.2% **Employment (%)** Employed: Overall N: 37.5% G1: 47.9% G2: 35.2% G3: 33.3% Retired: Overall N: 47.9% G1: 37.5% G2: 46.3% G3: 54.4%	**Other Theoretical model** = Self-efficacy theories also incorporated

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Pearce et al., 2008[39] Cardiovascular Risk Education and Social Support (CaRESS) Trial (continued)					Unemployed/ disabled: Overall N: 14.6% G1: 14.6% G2: 18.5% G3: 12.3% **Education (%)** ≤ Some high school: Overall N: 16.6% G1: 20.0% G2: 13.8% G3: 16.5% High school/GED: Overall N: 41.2% G1: 44.0% G2: 39.7% G3: 40.7% 2-year degree/some college: Overall N: 22.6% G1: 16.0% G2: 25.9% G3: 24.2% ≥ 4-year college graduate: Overall N: 19.6% G1: 20.0% G2: 20.7% G3: 18.7%	
Powell et al., 1995[40] NA	Overall N: NR G1: Mean (range) = 54 (20-94) G2: 55 (20-97)	Overall N: NR G1: 65% G2: 68%	NR	No	NA	**Funding source - Multiple** = Pharma (Merck & Co.) and corporate (Ciba-Geigy) **Theoretical model - Other** = NS

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Powers et al., 2011[68]	Overall N: 67 (8) G1: 68 (9) G2: 65 (8)	Overall N: 2% G1: 2% G2: 2%	**White** Overall N: 51% G1: 50% G2: 51% **Black** Overall N: 45% G1: 46% G2: 44%	Yes	**Self-reported medication nonadherence**, %: Overall N: 49% G1: 50% G2: 49% **Self-reported medication adherence** (Morisky scale), %: Overall N: NR G1: 50% G2: 51% **Diabetes**, %: Overall N:55% G1: 48% G2: 62% **CHD**, %: Overall N:44% G1: 48% G2: 40% **Atrial fibrillation**, %: Overall N:9% G1: 9% G2: 9% **Left ventricular hypertrophy**, %: Overall N:27% G1: 27% G2: 27%	NA

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Pyne et al., 2011[41] HIV Translating Initiatives for Depression Into Effective Solutions (HITIDES)	Overall N: 249 G1: 49.8(8.7) G2: 49.8(10.5)	Overall N: 7 G1: N: 3 G2: N: 4	**African American** Overall N: 155 G1: 63.4% G2: 61.6%	Yes	**Income greater than $20K:** G1: 60 (50.8%) G2: 52 (42.6%) **Physical health comorbidity score, mean (SD):** G1: 3.2 (2.3) G2: 3.8 (2.3) p=.046	col X: theory of Other
Rich et al., 1996[42] NA	Overall N: 80 (median) G1: 80.5 (6.7) G2: 78.4 (6.1) p: 0.029	Overall N: 67% G1: 74% G2: 59% p: 0.079	**Caucasian** Overall N: 35% G1: 40% G2: 29%	Yes	**Education > 8th grade, %:** Overall: NR G1: 60% G2: 51% **Hypertension, %:** Overall: NR G1: 81% G2: 83% **Diabetes, %:** Overall: NR G1: 25% G2: 32% **Prior heart failure, %:** G1: 68% G2: 82% p 0.067	**Other Theoretical model:** Not specified **Heart rate, mean**:* G1: 92 (+/- 20) G2: 83 (+/- 19) p: 0.004* **Hemoglobin (g/L), mean**: G1: 125 (+/- 18) G2: 120 (+/- 19) p: 0.087 **Creatinine (mmol/L), Mean**: G1: 137 +/- 66 G2: 158 +/- 83 p: 0.083 **Serum Cholesterol (mmol/L), mean:** G1: 5.3 +/- 1.3G2: 4.8 +/- 1.4 p: 0.052

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Rickles et al., 2005[43] NA	Overall N: 63 G1: 37.8 ± 10.7 G2: 37.5 ± 13.4	Overall N: G1: 25 (80.6%) G2: 28 (87.5%)	**White** Overall N: G1: 27 (87.1) G2: 31 (96.9) **Other:** Overall N: G1: 4 (12.9) G3:1 (3.1)	Yes	**Current number of medications other than antidepressants** Overall N: G1: 0.87 ± 1.41 G2: 0.78 ± 1.16 **No past history of psychiatric medication use, No. (%)** G1:18 (58.1) G2:27 (84.4) **Past use of psychiatric medications, No. (%)** G1:13 (41.9) G2: 5 (15.6) P<.05	**Other Teoretical Model** = health collaboration model

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Ross et al., 2004[44] NR	Overall N: NR G1: 57 (NR) G2: 55 (NR)	Overall N: NR G1: 20 G2: 26	**White, non-Hispanic** Overall N: NR G1: 92 G2: 88	Yes	**College graduate, %** Overall N: NR G1: 53 G2: 44 p <0.001 comparing participants to decliners (26% in decliners) **Household income<$45,000/year, %** Overall N: NR G1: 56 G2: 50 p <0.001 comparing participants to decliners (76% in decliners) **Safety net insurance program, %** Overall N: NR G1: 19 G2: 19 **Morisky BL score** Overall: 3.4 G1: NR G2: NR **GAS BL score:** Overall: 82 G1: NR G2: NR	**Other Theoretical model:** NS

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Rudd et al., 2004[45] NA	Overall N: NR G1: 59 (10) G2: 60 (9)	Overall N: NR G1: 50 G2: 56	**White** Overall N: NR G1: 76 G2: 72 **African American** Overall N: NR G1: 11 G2: 8 **Asian American** Overall N: NR G1: 4 G2: 4 **Hispanic** Overall N: NR G1: 1 G2: 8 **Other ethnicity** Overall N: NR G1: 8 G2: 8	Yes	**Some high school, %** Overall N: NR G1: 5 G2: 5 **High school graduate, %** Overall N: NR G1: 17 G2: 19 **Some college, %** Overall N: NR G1: 24 G2: 23 **College degree, %** Overall N: NR G1: 27 G2: 31 **Postdoctoral degree, %** Overall N: NR G1: 27 G2: 22 **Dyslipidemia, %** ($p<0.05$) Overall N: NR G1: 16 G2: 30	**Other Funding**: CorSolution's, Inc.

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Rudd et al., 2009[46] NA	Overall N: 127 G1: Mean 57.6 (13.8) G2: Mean 59.5 (13.9) p=0.43% ≥65 years old G1: 25% G2: 43% p: 0.03	Overall N: 127 G1: 81 G2: 78	**Caucasian** Overall N: 127 G1: 91 G2: 94	Yes	**Annual income <$30K** Overall N: 127 G1: 20% G2: 39% p=0.02	Other Study Design: RCT with stratified randomization based on education level.
Schaffer et al., 2004[47] NA	Overall N: 44 mean age 37 G1: NR G2: NR G3: NR G4: NR No statistical differences across groups	Overall N: 29/44 (65.9%) G1: NR G2: NR G3: NR G4: NR No statistical difference across groups	17% AA, 72% white, 1% Hispanic, Asian, or Pacific Islander; not reported by study arm; no statistical differences across groups	No	No baseline characteristics reported by study arm; however, across all study arms authors report that there were no statistical differences in years since asthma diagnosis, education, self-reported adherence, pharmacy-reported adherence, or baseline FEV1.	
Schectman et al., 1994[48] NA	Niacin Overall N: NR G1: 59 (1) G2: 62 (1) BAS Overall N: NR G1: 61 (2) G2: 59 (2)	Niacin Overall N: NR G1: NR G2: NR BAS Overall N: NR G1: NR G2: NR	**Caucasian** Niacin Overall N: NR G1: 86 G2: 90 **BAS** Overall N: NR G1: 86 G2: 82	Yes	**CHD, Diabetes, HTN, %** Niacin Overall N: NR G1: 39, 2, 56 G2: 42, 4, 63 **BAS** Overall N: NR G1: 35, 24, 62 G2: 37, 13, 52	**Multiple funding sources:** Gov't, Pharma (Squibb-Bristol) **Other Theoretical model:** NS
Schneider et al., 2008[49] NA	Overall N: 85 G1: 71.6 (5.9) G2: 72.3 (5.2)	Overall N: 85 G1: 24.7 G2: 25.9	Overall N: 85 G1: NR G2: NR	yes	**Renal impairment (SCr>1.2mg/dl)** Overall N: 85 G1: 6.5 G2: 7.9	

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Schnipper et al., 2006[50] NA	Overall N: 176 G1: 60.7 (17.2) G2: 57.7 (15.9)	Overall N: 176 G1: 67 G2: 65	Overall N: G1: NR G2: NR	No	NA	**Other Funding Source**: Pharma, university, Gov't
Simon et al., 2006[51] NA	Overall N: G1: 41±15 G2: 45±13	Overall N: G1: 71 (69%) G2: 63 (61%)	**White** Overall N: G1: 92 (89%) G2: 93 (89%)	Yes	**Severity: SCL depression scale** Overall N: G1: 1.61±.68 G2: 1.57±.71 **Patient Health Questionnaire score** (0 to 27 range; higher scores indicate more severe depression) G1: 16.0±6.2 G2: 15.8±6.1 95% CI, p: .84	**Other Funding Source:** funding from gov't and pharma **Other Theoretical Model**: NS

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Sledge et al., 2006[52] NA	Overall N: 96 G1: 53 (range 24-84) G2: 49 (range 23-80)	Overall N: 96 G1: 26 G2: 41	Overall N: 96 **Caucasian** G1: 32 G2: 31 **African American** G1: 49 G2: 51 **Hispanic** G1: 13 G2: 12	Yes	**Medicare/Medicaid** Overall N: 96 G1: 95% G2: 92% **Gross income <$20K** G1: 89% G2: 86% **Congestive heart failure** G1: 17% G2: 12% **Coronary artery disease** G1: 17% G2: 18% **COPD** G1: 23% G2: 16% **Diabetes mellitus** G1: 28% G2: 24% **ESRD/CRI** G1: 4% G2: 6% **Chronic pain** G1: 11% G2: 6% **Asthma** G1: 19% G2: 20%	**Other Funding Source:** Aetna health insurance company grant and Esther S. Gross Professorship **Other Conditions:** multiple conditions, NS

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Smith et al., 2008[53] NR	Overall: NR G1: 64.69 (14.19) G2: 65.04 (13.38)	Overall: NR G1: 31.3 G2: 34.0	NR	Yes	**Medicare, %** Overall: NR G1: 46.4 G2: 47.1 **Medicaid, %** Overall: NR G1: 1.6 G2: 1.6 **Adherence, Proportion of days covered in month before intervention, %** G1: 87 G2: 86	No theoretical model specified

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Solomon et al., 1998[54] NA Gourley et al., 1998[55] NA	Overall N (HTN); NR G1: 66.3 (10.0 SD) G2: 67.3 (11.0 SD) Overall (COPD): NR G1: 69.3 (5.9 SD) G2: 69.3 (9.2 SD)	Overall N (HTN): NR G1: 1.6% G2: 7.1% Overall (COPD): NR G1: 0 G2: 0	**Overall N (HTN)**: NR G1: Caucasian 61.9% Black 34.9% Asian 0 Hispanic 0 Missing 3.2% G2: Caucasian 65.7% Black 22.9% Asian 1.4% Hispanic 0 Missing 10.0% **Overall N (COPD)**: NR G1: Caucasian 90.7% Black 2.3% Asian 0 Hispanic 7.0% Missing 0 G2: Caucasian 83.6% Black 7.3% Asian 0 Hispanic 9.1% Missing 0	Yes	**Income**: **(HTN):** Overall: NR G1: $18,254 (12,259 SD) G2: $19,548 (16860 SD) **Income: (COPD):** Overall: NR G1: $20,908 (17,977 SD) G2: $21,022 (13,029 SD)	**Notes:** Medication adherence improved in hypertension arm; medication adherence did not improve in COPD arm (measures not reported in COPD arm)

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Stacy et al., 2009[56] NA	<50 yrs old (%) Overall N: 28.0 G1: 25.3 G2: 30.5 50-64 yrs old (%) Overall N: 62.4 G1: 64.4 G2: 60.2 65 yrs or older (%) Overall N: 9.7 G1: 9.0 G2: 10.3	Overall N: 62.4 G1: 62.1 G2: 62.7	Overall N: NR G1: NR G2: NR	Yes	**Mean of 3+ chronic medications dispensed =<90 days prior to index statin (%)** Overall N: 57.8 G1: 53.4 G2: 62.3 **Statin adherence: % started statin, never missed dose** Overall N: 72.9 G1: 71.5 G2: 74.1 **Statin adherence: % started statin, missed 1+ dose** Overall N: 21.9 G1: 22.1 G2: 21.7 **Statin adherence: % not yet started statin** Overall N: 5.2 G1: 6.3 G2: 4.2	Funding Source: NR
Taylor et al., 2003[57] NA	Overall N: 69 G1: 64.4 (13.7) G2: 66.7 (12.3)	Overall N: 69 G1: 63.6 G2: 72.2	**White** Overall N: 69% G1: 60.6 G2: 61.1	Yes	**Mean % (SD) adherent at BL (compliance scores ≥80%):** Overall N: 69 G1: 84.9 (6.7) G2: 88.9 (5.8)	**Other Conditions:** multiple conditions **Other Theoretical Model:** Principles of Pharmaceutical Care

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Vivian et al., 2002[58] NA	Overall N: NR G1: 64 (10.9) G2: 65.5 (7.8)	Overall N: NR G1: 0 G2: 0	**African American** Overall N: 77 G1: 84.6 G2: 70.4 **Caucasian** Overall N: 77 G1: 11.5 G2: 25.9	Yes	**Diabetes, %** Overall N: NR G1: 42 G2: 59	**Other Theoretical model:** not specified
Waalen et al., 2009[59] NA	Overall N: 237 G1: 71.3 (7.3) G2: 70.5 (12.6)	Overall N: 237 G1: 100% G2: 100%	**White** Overall N: 237 G1: 91.2 G2: 98.2 **Hispanic** Overall N: 237 G1: 2.4 G2: 0.9 **Asian** Overall N: 237 G1: 5.6 G2: 0.9 **Black** G1: 0.8 G2: 0	No	NA	NA.

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Wakefield et al., 2011[60] NA	Overall N: 68 (10) G1: 67.8 (10) G2: 68.4 (9.5) G3: 69.9 (9.9)	Overall N: 2% G1: 1% G2: 1% G3: 4%	**American Indian/Alaska Native** Overall N: NR G1: 0% G2: <1% G3: 2% **Black/African American** Overall N: NR G1: 3% G2: 2% G3:<1% **Hispanic** Overall N:NR G1: 0% G2: <1% G3: <1% **White** Overall N: 96% G1: 97% G2: 96% G3 95%	No	NA	NA
Weinberger et al., 2002[61] NA	COPD: mean (SD) Overall N: 453 G1: 62.2 (11.0) G2: 62.9 (10.3) G3:62.2 (11.9) Asthma: Overall N: 660 G1: 44.7 (14.2) G2: 46.6 (15.1) G3:44.6 (15.5)	COPD: number (%) Overall N: 453 G1:118 (63.8) G2: 86 (66.2) G3:93 (67.4) Asthma: Overall N: 660 G1: 210 (80.2) G2: 190 (81.6) G3:139 (84.2)	**White**, % COPD: number (%) Overall N: 453 G1:149 (80.5) G2: 116 (89.2) G3:127 (92.0) Asthma: Overall N: 660 G1: 197 (75.2) G2: 189 (81.1) G3:145 (87.9)	Yes	**Medication compliance, No (%) not compliant** COPD Overall N: 453 G1: 64 (34.8) G2: 46 (35.4) G3: 54 (39.0) Asthma: Overall N: 660 G1: 91 (34.7) G2: 77 (33.1) G3: 61 (37.2)	**Other Randomization**: randomization was stratified within cluster of 3 proximal drugstores **Other Theoretical Model**: not reported

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Weinberger et al., 2002[61] NA (continued)			within both conditions, race differed by group (p<0.05)		**Med compliance - 4 item measure, mean SD** COPD Overall N: 453 G1: 1.3 (1.2) G2: 1.1 (1.0) G3: 1.0 (1.1) Asthma Overall N: 660 G1: 1.4 (1.1) G2: 1.2 (1.1) G3: 1.4 (1.2) **Peak expiratory flow rates (PEFR), mean SD, % predicted** COPD: Overall N: 453 G1: 52.1 (21.1) G2:46.4 (19.8) G3:48.1 (18.4) p<.05 Asthma: Overall N: 660 G1:70.0 (18.0) G2:69.5 (18.5) G3:70.8 (19.2) p>=.05	**Note**: baseline characteristics presented stratified by disease (COPD vs.asthma)

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Weymiller et al., 2007[62] Statin Choice Randomized Trial Jones et al., 2009[63] Statin Choice Randomized Trial	Overall N: Mean (SD) = NR G1: Mean (SD) = 64 (12) G2: Mean (SD) = 66 (8) Overall N: Mean (SD) = NR G1: Mean (SD) = 65.4 (11.1) G2: Mean (SD) = 63.4 (12.7) G3: Mean (SD) = 67.4 (8.0) G4: Mean (SD) = 65.8 (8.1)	Overall N: NR G1: 31% G2: 57% Overall N: NR G1: 26.9% G2: 34.6% G3: 56.5% G4: 56.5%	NR	Yes	**Diagnosis of CAD** G1: N (%) = 26 (50%) G2: N (%) = 20 (43%) **United Kingdom Prospective Diabetes Study (UKPDS) estimated 10-year Cardiovascular risk** **<15%** G1: N (%) = 6 (12%) G2: N (%) = 15 (33%) **15-30%** G1: N (%) = 16 (31%) G2: N (%) = 7 (15%) **>30%** G1: N (%) = 30 (58%) G2: N (%) = 24 (52%) **Diagnosis of CAD** G1: N (%) = 15 (57.7%)	**Other** **Randomization** = Providers were randomized to treatment or control, and patients were randomized to receive the intervention or control materials either from their clinician during the visit or from a researcher before the visit **Funding source - Multiple** = Foundation/non-profit and Mayo Clinic-affiliated patient education center **Other** **Theoretical model** - Other = NS **BL characteristics - Other** =High school education completed Overall N: NR G1: N (%) = 51 (98%) G2: N (%) = 39 (87%) High school education Overall N: NR G1: N (%) = 25 (96.2%) G2: N (%) = 26 (100.0%)

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Weymiller et al., 2007[62] Statin Choice Randomized Trial Jones et al., 2009[63] Statin Choice Randomized Trial (continued)					**UKPDS estimated 10-year cardiovascular risk<15%** G1: N (%) = 4 (15.4%) G2: N (%) = 2 (7.7%) G3: N (%) = 8 (34.8%) G4: N (%) = 7 (30.4%) **15-30%** G1: N (%) = 7 (26.9%) G2: N (%) = 9 (34.6%) G3: N (%) = 5 (21.7%) G4: N (%) = 2 (8.7%) **>30%** G1: N (%) = 15 (57.7%) G2: N (%) = 15 (57.7%) G3: N (%) = 10 (43.5%) G4: N (%) = 14 (60.9%)	G3: N (%) = 22 (95.7%) G4: N (%) = 17 (77.3%)

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Williams et al., 2010[64] NA	Overall N: 2698 G1: 26.8 +/- 17.4 G2: 28.8 +/- 17.4	Overall N: 1490 G1: 737 (55.2%) G2: 753 (55.3%)	**African American** Overall N: 1039 G1: 511 (38.3) G2: 528 (38.7) **White** Overall N: 1475 G1: 726 (54.4) G2: 749 (55.0) **Other** Overall N: 184 G1: 98 (7.3) G2: 86 (6.3)	No	NA	**Other Theoretical model**: none **Other randomization**: clustered randomization was stratified by type of clinical practice: pediatrics vs. family medicine and internal medicine **Notes:** Usual care group was given extensive educational materials in a variety of formats. G1 providers given opportunity to access adherence data in addition.

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Wilson et al., 2010[65] Better Outcomes of Asthma Treatment (BOAT); note that there is online supplemental material for methods and timeline	Overall N:612 G1: 45.7 +/- 13.3 G2: 46.9 +/- 12.1 G3: 45.1 +/- 12.4	Overall N: G1: 115 (56.4) G2: 114 (55.9) G3: 117 (57.4)	**Caucasian** G1: 128 (62.8) G2: 124 (60.8) G3: 127 (62.3) AA G1: 32 (15.7) G2: 34 (16.7) G3: 30 (14.7) **Asian** G1: 20 (9.8) G2: 18 (8.8) G3: 22 (10.8) Hispanic G1: 9 (4.4) G2: 9 (4.4) G3: 8 (3.9) **Pacific Islander** G1: 15 (7.4) G2: 16 (7.8) G3: 17 (8.3) **American Indian** G1: 0 (0.0) G2: 3 (1.5) G3: 0 (0.0)	Yes	**Severity Level of Asthma control:** Very poorly controlled G1: 79 (38.7) G2: 82 (40.2) G3: 85 (42.1) Poorly controlled: G1: 96 (47.1) G2: 87 (42.7) G3: 83 (41.1) Moderately well controlled: G1: 17 (8.3) G2: 24 (11.8) G3: 29 (14.4) Well controlled: G1: 12 (5.9) G2: 11 (5.4) G3: 5 (2.5) **Hospitalized for asthma in past 2 years** G1:71 (34.8) G2: 69 (33.8) G3: 76 (37.3) **Income >/=40K/yr** G1: 133 (66.8) G2: 139 (70.9) G3: 134 (69.1)	NA

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Wolever et al., 2010[66] NA	Overall N: 53 (7.93) G1: 53.1 (8.29) G2: 52.8 (7.64)	Overall N: 77% G1: 73% G2: 81%	**White** Overall N: 39% G1: 33% G2: 46% **Black** Overall N: 57% G1: 63% G2: 50% **Other** Overall N: 4% G1: 3% G2: 4%	Yes	**Household income < $50,000** Overall N: 55% G1: 57% G2: 54% **Household income ≥ $50,000** Overall N: 45% G1: 43% G2: 46%	**Theoretical model - other** = Integrative health coaching
Zhang et al., 2010[67] NA	**Hyperlipidemia** (N = 9185): G1 (Age %): 65-74 years, 40.2%; 75-84 years, 53.6%; ≥85 years, 6.2% G2 (Age %): 65-74 years, 52.4%; 75-84 years, 41.1%; ≥85 years, 6.5% G3 (Age %): 65-74 years, 54.7%; 75-84 years, 40.3%; ≥85 years, 5% G4 (Age %): 65-74 years, 62%; 75-84 years, 34.3%; ≥85 years, 3.7%	**Hyperlipidemia**: G1: 68.4 G2: 65.4 G3: 61.5 G4: 50.9 **Diabetes** G1: 60.3 G2: 58.2 G3: 56.7 G4: 47.6 **Hypertension** G1: 69.3 G2: 66.4 G3: 64.7 G4: 53.8 G4 differs from G1, G2, and G3 at p < 0.05	**Hyperlipidemia: Proportion of white beneficiaries** G1: 92.3 G2: 96 G3: 92 G4: 92.2 G2 vs. G4, p < 0.05 **Diabetes: Proportion of white beneficiaries** G1: 92.8 G2: 96.2 G3: 92.1 G4: 91.5 G2 vs. G4, p < 0.05 **Hypertension: Proportion of white beneficiaries** G1: 91.6 G2: 96.0 G3: 91.6 G4: 91.7 G2 vs. G4, p < 0.05	Yes	**Hyperlipidemia**: Median Income ($), mean (SE) Among 65-74 year olds G1: 26,440 (261) G2: 25,865 (153) G3: 28,782 (92) G4: 28,948 (118) Among >75 year olds G1: 19,798 (200) G2: 19,124 (123) G3: 20,796 (63) G4: 20,992 (79) Proportion living in Urban areas G1: 72.1 G2: 60.5 G3: 80 G4: 80.2 G1 and G2 differ from G4 at p < 0.05	**Other level of randomization** = NA **Multiple funders** = government, nonprofit, and academic **Other theoretical model** = NS

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Zhang et al., 2010[67] NA (continued)	**Diabetes** (N = 4018) G1 (Age %): 65-74 years, 41.3%; 75-84 years, 49.8%; ≥85 years, 8.9% G2 (Age %): 65-74 years, 50%; 75-84 years, 42.8%; ≥85 years, 7.2% G3 (Age %): 65-74 years, 54%; 75-84 years, 39.7%; ≥85 years, 6.3% G4 (Age %): 65-74 years, 60.7%; 75-84 years, 34.9%; ≥85 years, 4.5% **Hypertension** (N = 14,735) G1 (Age %): 65-74 years, 37.3%; 75-84 years, 48.6%; ≥85 years, 14.1% G2 (Age %): 65-74 years, 44.7%; 75-84 years, 44.6%; >85 years, 10.8% G3 (Age %): 65-74 years, 48.1%; 75-84 years, 42.5%; >85 years, 9.4%				**Diabetes** Median Income ($). Mean (SE) Among 65-74 year olds G1: 26,740 (361) G2: 25,713 (207) G3: 27,854 (130) G4: 28,611 (178) Among >75 year olds G1: 19,968 (260) G2: 19,024 (167) G3: 20,290 (92) G4: 20,642 (113) Proportion living in Urban areas G1: 74.1 G2: 58.5 G3: 77.5 G4: 77.6 G2 vs. G4, $p < .05$ **Hypertension** Median Income ($), mean (SE) Among 65-74 year olds G1: 26,940 (182) G2: 25,784 (107) G3: 28,427 (71) G4: 28,688 (100) Among >75 year olds G1: 19,868 (128) G2: 19,168 (89) G3: 20,563 (47) G4: 20,875 (67)	

Author, Year Trial Name	Baseline Age - Mean (SD)	Baseline % Female	Race/Ethnicity %	Other Baseline Characteristics Reported	Specify Characteristic and Group Differences	Add Comments or Specify "Other" Entries
Zhang et al., 2010[67] NA (continued)	G4 (Age %): 65-74 years, 55.9%; 75-84 years, 37.9%; >85 years, 6.2% G4 differs from G1, G2, and G3 at $p < 0.05$				Proportion living in Urban areas G1: 75.4 G2: 57.9 G3: 79.7 G4: 80.3 G2 vs. G4, $p < 0.05$	

Table D9. Medication adherence outcomes 1

Author, Year Trial Name	Medication Adherence Outcome 1	Description of Timing of Measurement of Adherence Outcome 1	Data Source	N	Results
Bender et al., 2010[1] NA	Percent adherence was determined by dividing the number of inhaler puffs taken by the number of puffs prescribed to be taken each day and then averaged over the 10-week interval	10 weeks, measured once for entire period	Other	G1: 25 G2: 25	Mean % (SD): G1: 64.5% (17.2) G2: 49.1% (16.8) F: 9.66 p: .0032
Berg et al., 1997[2] NA	Compliance measured as a mean of number of events recorded on Chronolog inhaler vs. number of expected events based on self-report of prescription (SD)Source of data is a combination of self-report and MDI chronolog scores	Compliance calculated as a % each day at week 7	Other	G1: 31 G2: 24	G1: 49 (31) G2: 32 (28) 95% CI, NR p<0.05
Berger et al., 2005[3] NA	Discontinued use of Avonex	Assessed at 3 months	Self-report	G1: 172 G2: 195	G1: 2 (1.2%) discontinued G2: 17 (8.7%) discontinued 95% CI, NR p: 0.001
Bogner et al., 2008[4] NA	Depression adherence: % of prescribed doses taken; calculated as number of doses taken divided by the number of doses prescribed during the observation period multiplied by 100% - dichotomized with 80% threshold	Measured over 6 week study period for entire study period	MEMS	G1: 32 G2: 32	G1: 23 (71.9) G2: 10 (31.3) 95% CI, p: .001
Bogner et al., 2010[5] NA	>80% adherence to an oral hypoglycemic agent	4 times, biweekly beginning at baseline and ending at week 6	MEMS	G1: 29 G2: 29	**BL** G1: 10 (34.5%) G2: 6 (20.7%) 95% CI, NR p: 0.19 **EP at 6 weeks** G1: 18 (62.1%) G2: 7 (24.1%) 95% CI, NR p: 0.004
Bosworth et al., 2005[6] V-STITCH	Change in proportion reporting overall medication adherence at 6 months between G1 and G2	Last 6 months; 2 times (including baseline); 6 months	Self-report	G1: NR G2: NR	0.0074 95% CI, -0.062 to 0.076 p: NR

Author, Year Trial Name	Medication Adherence Outcome 1	Description of Timing of Measurement of Adherence Outcome 1	Data Source	N	Results
Bosworth et al., 2008[7] TCYB Bosworth et al., 2007[8] TCYB Methods paper	Increase in self-reported adherence from baseline to 6 months	Last 6 months; 1 time; 6 months	Self-report	G1: 319 G2: 317	G1: +9% (63% to 72%) G2: +1% (67% to 68%) p=NR
Capoccia et al., 2004[9] na	Adherence to antidepressants - at 3 mo	Defined as use of antidepressants for at least 25 of the past 30 days; measured at 3, 6, 9, 12 mos	Self-report	G1: NR G2: NR	G1: 85% G2: 81% 95% CI, NR Not Significant
Carter et al., 2009[10] NA	Percentage of patients with low self-reported medication adherence (i.e., score ≥3)	Measured twice, once at baseline & once at 6 month follow-up	Self-report	G1: 192 G2: 210	**BL (Mean %, SD)** G1: 17.3% (27.5) G2: 18.7% (22.0) 95% CI, NR **6 month follow-up (Mean %, SD)** G1: 14.6% (25.4) G2: 14.7% (20.9) 95% CI, NR P (within-group): 0.602 G2 P (within-group): 0.979 G1
Chernew et al., 2008[11] NA	Medication Possession Ratio (MPR is number of eligible days in the quarter the person was in possession of the medication divided by the number of days in the quarter)	Measured in the pre and post periods (eight observations per patient during 2-year period)	Other	**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	**Effect size (percent MPR Points)** **ACE inhibitors/ARB** = 2.59, p<0.001 **Beta-blockers** = 3.02, p<0.001 **Diabetes drugs** = 4.02, p<0.001 **Statins** = 3.39, p<0.001 **Steroids** = 1.86, p<0.134

Author, Year Trial Name	Medication Adherence Outcome 1	Description of Timing of Measurement of Adherence Outcome 1	Data Source	N	Results
Choudhry et al., 2010[12] NA	Proportion of days covered (i.e., estimated number of days of medication available to each patient) - Change in level (i.e., immediate impact of copayment policy)	Measured monthly over the 24-month study period	Other	Overall N: 52,631 G1: 2051 G2: 779 G3: 38,174 G4: 11,627	Statin users Adjusted for differences in comorbidity & demographics G1: 3.1% increase in monthly adherence over G3, with no subsequent change in slope 95% CI, NR p: <0.05 Matched by first fill date for eligible prescription in study timeframe G1: 2.6% increase over G3, with no subsequent change in slope p: <0.05 Clopidogrel users Adjusted (all patients) G2: 4.2% increase over G4, with no subsequent change in slope 95% CI, NR p: <0.05 Matched by first fill date for eligible prescription in study timeframe G1: 6.6% increase over G4, with no subsequent change in slope 95% CI, NR p: <0.05

Author, Year Trial Name	Medication Adherence Outcome 1	Description of Timing of Measurement of Adherence Outcome 1	Data Source	N	Results
Choudhry et al., 2011[13]	Mean medication possession ratio (among all patients)	Number of days for which patients had a supply of each medication class available divided by the # days they were eligible for that medication. Patients who lost eligibility before randomization or who did not fill a prescription after randomization were considered to be nonadherent.	Prescription claims records	G1: 2845 G2: 3010	**All 3 medication classes** G1: 43.9 (33.7) G2: 38.9 (32.7) 95% CI, 5.4 (3.6-7.2) p: <0.001 **ACE inhibitor or ARB** G1: 41.1 (39.8) G2: 35.9 (38.1) 95% CI, 5.6 (3.4-7.7) p: <0.001 **Beta-blocker** G1:49.3 (37.5) G2: 45.0 (36.6) 95% CI, 4.4 (2.3-6.5) p: <0.001 **Statin** G1: 55.1 (37.7) G2: 49.0 (37.3) 95% CI, 6.2 (3.9-8.5) p: <0.001
Friedman et al., 1996[14] NA	Antihypertensive medication adherence (total number of tablets, capsules, or patches dispensed minus the total number counted in the audit, divided by the number that should have been taken by each subject)	Change scores were computed using value at 6 months minus value at baseline	Pill count	G1: 133 G2: 134	Unadjusted change from BL G1: 2.4% mean increase G2: 0.4% mean increase p= 0.29 Adjusted change from BL G1: 17.7% mean increase G2: 11.7% mean increase p= 0.03

Author, Year Trial Name	Medication Adherence Outcome 1	Description of Timing of Measurement of Adherence Outcome 1	Data Source	N	Results
Fulmer et al., 1999[15] NA	Percent of prescribed medication doses taken	Adherence was monitored during a 2-week pre-intervention phase, 6-week intervention phase (time 2), and 2-week post-intervention phase (time 3)	MEMS	G1: 17 G2: 15 G3: 18	**Average compliance rates at BL** G1: 82% G2: 76% G3: 81% **Average compliance rates at time 3** G1: 84% G2: 74% G3: 57% (significantly decreased from baseline at p<0.04) 95% CI, p: There was a statistically significant time effect during the course of the study from baseline to post-intervention (F=4.08, p<0.05). Over time, G1 and G2 showed enhanced compliance relative to G3. However, there was no significant difference between G1 and G2.
Grant et al., 2003[16] NA	Difference from baseline to 3-month follow up in number of days in the last 7 that no doses were missed	7 days; two measures; baseline and 3 months measures	Self-report	G1: 61 G2: 54	G1: 0.1 (1) G2: 0.1 (0.4) 95% CI, p: 0.8
Guthrie et al., 2001[17] First Myocardial Infarction (MI) Risk Reduction Program	Medication compliance survey: patient currently taking pravastatin as prescribed, %	NR; 2 times; 3 months	Self-report	G1: 3635 G2: 913	At 6 months G1: 79.7 G2: 77.4 95% CI, NR p: NR
Hoffman et al., 2003[18] NA	Percent adherence, first observation after 1 month of therapy	Patients with < 10 gap days in the initial month of therapy; measured once at 1 month	PRD	G1: 4899 G2: 4665	G1: 58.9 G2: 57.4 95% CI, NR p: 0.136

Author, Year Trial Name	Medication Adherence Outcome 1	Description of Timing of Measurement of Adherence Outcome 1	Data Source	N	Results
Hunt et al., 2008[19] NA	Proportion of subjects reporting high medication adherence at study end	One time at end of study	Self-report	G1: 142 G2: 130	G1: 67% (N = 95/142) G2: 69% (N = 90/130) 95% CI, NR p: 0.771
Janson et al., 2009[21] NA	Mean change % adherence; numerator was capped at the prescribed doses per day to avoid overestimation of adherence to greater than 100% per day. Percent adherence (taken/prescribed)	Measured biweekly during 4-week intervention (T0-T1); measured at 4-week intervals for following 14 weeks of observation (T1-T2)	Other	NR	**T0-T1** G1: -0.18 G2: -1.40 p: 0.72 **T1-T2** G1: -4.28 G2: -4.41 p: 0.97
Janson et al., 2003[20] NA	ICS adherence (number of puffs recorded daily in the diary divided by the number of puffs prescribed) % (SD) Source of data was self-report supplemented by medication monitors	Assessed at baseline, and end of week 1, 2, 5, 7; time frame for baseline measurement was one week; time frame for final measurement NR	Other	G1: 33 G2: 32	G1: 91 (32) G2: 62 (38) 95% CI, NR p: NR
Johnson et al., 2006[23] NR	Behavioral measure of non-adherence [Data source: 5-item survey measuring frequency of various form of non-adherence]	Last 6 months; 4 times every 6 months (0,6,12, and 18 months)	Self-report	G1: NR G2: NR	**BL** G1: in figure only G2: in figure only 95% CI, NR P>0.05 **6 months** G1: in figure only G2: in figure only 95% CI, NR P>0.05 **12 months** G1: in figure only G2: in figure only 95% CI, NR P<0.01 **18 months** G1: in figure only G2: in figure only 95% CI, NR P<0.001

Author, Year Trial Name	Medication Adherence Outcome 1	Description of Timing of Measurement of Adherence Outcome 1	Data Source	N	Results
Johnson et al., 2006[22] NR	Pre-action sample only Reaching Action (A) or M (Maintenance) stage for adherence, % [Data source: complete case analysis evaluating Stage of Change]	Last 6 months; 4 times every 6 months (0,6,12, and 18 months)	Self-report	**BL** Overall N: 205 G1: NR G2: NR **6 months** Overall N: 190 G1: NR G2:NR **12 months** Overall N: 172 G1: NR G2: NR **18 months** Overall N: 173 G1:NR G2: NR	**BL** G1: in figure only G2: in figure only OR: NR p:NR **6 months** G1: 55.3% G2: 40.0% OR=1.80 P<0.05 **12 months** G1: in figure only G2: in figure only OR: NR p=0.057 **18 months** G1: 56.0% G2: 37.8% OR: NR P<0.01
Katon et al., 1995[24] NA	% receiving adequate dosage of antidepressants for ≥30 days (details NR)	During continuation phase of treatment (3-7 months)	PRD	**Major depression group** N=91 **Minor depression group** N=126	**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
Katon et al., 1996[25] NA	Medication adherence - telephone interview asking if they were still taking antidepressants and considered adherent if they reported taking medication at least 25 out of last 30 days	Measured at 1-month follow up	Other: self-report, verified with data from pharmacy refills, at 1 and 4 months the K statistic was 0.83 and 0.90 respectively.	G1: 76 G2: NR	**Major Depression Group at 1-month follow up (% adherent)** G1: 85%G2: 63%p=0.06 **Minor Depression Group at 1-month follow up (% adherent)** G1: 81%G2: 67%p=.13

Author, Year Trial Name	Medication Adherence Outcome 1	Description of Timing of Measurement of Adherence Outcome 1	Data Source	N	Results
Katon et al., 1999[26] NA Katon et al., 2002[27] NA	Percent adherent to antidepressant medication	Patients report medication adherence; questions asked not specified. Considered adherent if medication taken for at least 25 of the previous 30 days; assessed at 1, 3, and 6 months(Reported in 9123)	Self-report	G1: 114 G2: 114	**At 1-month** G1: 77.4% G2: 69.2% Chi-square: 1.38 p: 0.24 **At 3 months**: G1: 78.6% G2: 62.1% Chi-square: 5.52 p: 0.02 **At 6 months**: G1: 73.2% G2: 50.5% Chi-square: 9.53 p: 0.002
Katon et al., 2001[28] NA Ludman et al., 2003[29] NA Van Korff et al., 2003[30] NA	Percent patients who filled AD prescriptions (Katon et al.)	Measured at 3, 6, 9, 12 months	PRD	G1: NR G2: NR	**Across 12-months**: Adjusted OR forG1:G2, 1.91 95% CI, (1.37, 2.65) p: < 0.001% patients (95% CI) **0-3 m**: G1: 80.7 (75.1-86.3) G2: 65.6 (58.8-72.4) **3-6m**: G1: 71.9 (65.5-78.2) G2: 58.2 (51.2-65.2) **6-9m**: G1: 68.4 (61.8-75.0) G2: 55.6 (48.5-62.7) **9-12m**: G1: 63.2 (53.3-70.0) G2: 49.7 (42.6-56.9)
Lee et al., 2006[31] FAME	% medication adherence at 14 months (proportion of pills taken), mean (SD)	Total timeframe of 6 month average (months 8-14); G1 - 3 pill counts every 2 months; G2 - 1 pill count at the end of 6 months	Pill count	G1: 83 G2: 76	G1: 95.5 (7.7) G2: 69.1 (16.4) 95% CI, NR P<0.001

Author, Year Trial Name	Medication Adherence Outcome 1	Description of Timing of Measurement of Adherence Outcome 1	Data Source	N	Results
Lin et al., 2006[32] NA	Percentage of days nonadherent	Measured 2 times over a 12-month period	PRD	Oral hypoglycemic agent **BL** G1: 103 G2: 103 **EP** G1: 103 G2: 103 ACE inhibitor **BL** G1: 54 G2: 65 **EP** G1: 59 G2: 52 Lipid-lowering agent **BL** G1: 50 G2: 52 **EP** G1: 54 G2: 63	Oral hypoglycemic agent **BL** (%) (Mean (SD)) G1: 19.8% (21.3%) G2: 22.9% (24.0%) 95% CI, NR p: NS **EP** (%) (Mean (SD)) G1: 28.2% (28.9%) G2: 24.0% (24.7%) 95% CI, NR p: <0.03 ACE inhibitor **BL** (%) (Mean (SD)) G1: 27.4% (27.1%) G2: 29.7% (29.3%) 95% CI, NR p: NS **EP** (%) (Mean (SD)) G1: 24.2% (22.7%) G2: 18.9% (17.4%) 95% CI, NR p: NS Lipid-lowering agent **BL** (%) (Mean (SD)) G1: 29.3% (26.7%) G2: 24.5% (23.0%) 95% CI, NR p: NS **EP** (%) (Mean (SD)) G1: 28.8% (27.1%) G2: 27.7% (24.0%) 95% CI, NR p: NS

Author, Year Trial Name	Medication Adherence Outcome 1	Description of Timing of Measurement of Adherence Outcome 1	Data Source	N	Results
Maciejewski et al., 2010[33]	Percent change in medication possession ratio (MPR) from baseline (adherence differences between G1 and G2) Unmatched analysis	24 monthly assessments: 12 in the pre-intervention period and 12 in the post-period	Other	**Diuretics** Overall N: NR G1: 15605 G2: 9137 **ACE Inhibitors** Overall N: NR G1: 14250 G2: 7668 **Statins** Overall N: NR G1: 18346 G2: 10162 **Beta Blockers** Overall N: NR G1: 11137 G2: 6343 **Calcium Channel Blockers** Overall N: NR G1: 7191 G2: 4099 **Metformin** Overall N: NR G1: 5077 G2: 2826 **ARBS** Overall N: NR G1: 7445 G2: 4514 **Cholesterol Absorption Inhibitors** Overall N: NR G1: 4019 G2: 2291	**Metformin**: 3.80% p: <0.001 **Diuretics**: 3.26% p: <0.001 **ACE inhibitors**: 2.87% p: <0.001 **Beta-blockers**: 2.48% p: <0.001 **Statins**: 1.81% p: <0.001 **Calcium-channel blockers**: 1.46% p: <0.01 **ARBS:** -0.10% p: NS **Cholesterol absorption inhibitors**: -1.04% p: NS

Author, Year Trial Name	Medication Adherence Outcome 1	Description of Timing of Measurement of Adherence Outcome 1	Data Source	N	Results
Mann et al., 2010[34] The Statin Choice	% of participants with good adherence at 3 months using Morisky 8-item scale (NOTE: calculated % with "good adherence" without information re: how this was defined using the scale; other studies have used cut-off of <6)	Ever, yesterday, 2 weeks, sometimes (used Morisky 8-item scale which uses all these time frames); measured TWICE; at 3 and 6 months over the phone;	Self-report	G1: NR G2: NR	G1: NR G2: NR 95% CI, p: No significant difference reported between groups for overall 70% with "good adherence" for whole group at 3 months
Montori et al., 2011[35]	Adherence: >80% days covered	Measured at 6 months	PRD	G1: 23 G2: 19	G1: 100% G2: 74% 95% CI, NR p: 0.009
Murray et al., 2007[36] NA	"Taking Adherence": % of prescribed medication doses taken based on physician's prescription	During intervention period (9 mos)Frequency: continuous daily MEMS monitoringDuration between measures: 12 to 24 hours, depending on med frequency	MEMS	G1: 122 G2: 192	Proportion (95% CI) G1: 78.8% (74.9-82.7) G2: 67.9% (63.8-72.1) Difference: 10.9% (5.0-16.7) p: NR
Nietert et al., 2009[37] NA	Time-to-refill (days)	NR	PRD	G1: 1018 G2: 1016 G3: 1014	Unadjusted G1: Median (interquartile range or IR) = 108 (39-257) G2: Median (IR) = 116 (37-257) G3: Median (IR) = 106 (31-257) (257 represents a lower bound than 75th percentile because of amount of censoring present) 95% CI, NR p: NR Adjusted G1: Hazard ratio (HR, 97.5% CI) = 0.93 (0.82-1.06) G2: HR, 98.3% CI = 0.87 (0.76-1.00) G3: HR, 95% CI = 0.93 (0.83-1.05) 95% CI, NR p: NR

Author, Year Trial Name	Medication Adherence Outcome 1	Description of Timing of Measurement of Adherence Outcome 1	Data Source	N	Results
Okeke et al., 2009[38] NA	Proportion of prescribed doses taken	Dosing aids were 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)	Other	G1: 35 G2: 31	G1: adherence rate (SD) 0.73 (0.22) G2: adherence rate (SD) 0.51 (0.30) 95% CI, NR p: 0.001
Pearce et al., 2008[39] Cardiovascular Risk Education and Social Support (CaRESS) Trial	Medication adherence (unspecified)	3 times for G2, and 2 times for G1 and G3 over a 12-month period	Self-report	G1: 50 G2: 58 G3: 91	**BL** 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 **EP** High (%): G1: NR, G2: NR, G3: NR Medium (%): G1: NR, G2: NR, G3: NR Low (%): G1: NR, G2: NR, G3: NR

Author, Year Trial Name	Medication Adherence Outcome 1	Description of Timing of Measurement of Adherence Outcome 1	Data Source	N	Results
Powell et al., 1995[40] NA	Medication possession ratio (MPR)	Refill data collected over a 9-month period	PRD	G1: 1993 G2: 2253	**Overall** G1: 0.70 (0.23) G2: 0.70 (0.28) 95% CI, NR p: NR **Benazepril** (Mean (SD)) G1: 0.71 (0.25) G2: 0.72 (0.26) 95% CI, NR p: NR **Transdermal estrogen** (Mean (SD)) G1: 0.60 (0.32) G2: 0.58 (0.32) 95% CI, NR p: NR **Metoprolol** (Mean (SD)) G1: 0.74 (0.27) G2: 0.73 (0.28) 95% CI, NR p: NR **Simvastatin** (Mean (SD)) G1: 0.73 (0.26) G2: 0.70 (0.28) 95% CI, NR p: NR
Powers et al., 2011[68]	Self reported med adherence measured by Morisky scale	3 months; 1 time; 3 months	Self-report	G1: 44 G2: 45	G1: 46% G2: 49% 95% CI, NR p: 0.55

Author, Year Trial Name	Medication Adherence Outcome 1	Description of Timing of Measurement of Adherence Outcome 1	Data Source	N	Results
Pyne et al., 2011[41] HIV Translating Initiatives for Depression Into Effective Solutions (HITIDES)	Antidepressant regimen adherence - at 6 months;	Each measurement is percentage adherence over previous 4 days (i.e. total number of prescribed pills taken divided by total number of prescribed; transformed to dichotomous outcome with cutpoint at >=80%). 3 measurements taken: baseline, 6-month and 12-months.	Self-report	G1: 66 G2: 72	G1: 78.8% G2: 69.4% OR (95%CI): 1.60 (0.74 to 3.45) Adjusted OR (95%CI): 1.65 (0.75 to 3.62) Adjusted p: 0.22
Rich et al., 1996[42] NA	Overall compliance rates by method 1: percentage of pills taken correctly for each current medication determined by pill count at home visit by pharmacist or trained pharmacy assistant, then averaged	30 days +/- 2 days after discharge; 1 time; NA	Pill count	G1: 80 G2: 76	Overall: 84.6% +/- 15.1% G1: 87.9 +/- 12.0% G2: 81.1 +/- 17.2% 95% CI, NR p: 0.003
Rickles et al., 2005[43] NA	% omitted antidepressant doses at 3 months	2 measurements, each for 3 month time period	PRD	G1: 28 G2: 32	N (Mean ± SD) G1: 28 (18.1 ± 23.5) G2: 32 (18.7 ± 22.1) NS
Ross et al., 2004[44] NR	Medication adherence score (scored 0-4)[questions derived from Morisky]	NR; 3 times (including baseline); 6 months	Self-report	G1: NR G2: NR	**6 months** G1: 3.5 G2: 3.4 Difference (CI): +0.1 (-0.2 to 0.4) p: NR **12 months** G1: 3.6 G2: 3.4 Difference (CI): +0.2 (-0.1 to 0.6) p: 0.15
Rudd et al., 2004[45] NA	Rate of daily adherence (average number of days on which patient's took the correct number of doses as prescribed) at 6 months, mean (SD)	1 day; daily ; 6 months	MEMS	G1: NR G2: NR	G1: 80.5% (23.0%) G2: 69.2% (31.1%) 95% CI, NR p: 0.03

Author, Year Trial Name	Medication Adherence Outcome 1	Description of Timing of Measurement of Adherence Outcome 1	Data Source	N	Results
Rudd et al., 2009[46] NA	Mean score on adherence to treatments scale (0=best, 3=worst)	Measured at baseline, 6 and 12 months; self-report period NR	Self-report	**BL** G1: 51 G2: 63 **6 mos** G1: 49 G2: 57 **12 mos** G1: 48 G2: 57	**BL** mean (SD) score (0=best, 3=worst) G1: 0.40 (0.40) G2: 0.30 (0.37) **6 mos** mean (SD) G1: 0.23 (0.28) G2: 0.24 (0.32) **12 mos** mean (SD) G1: 0.17 (0.25) G2: 0.18 (0.30)

Author, Year Trial Name	Medication Adherence Outcome 1	Description of Timing of Measurement of Adherence Outcome 1	Data Source	N	Results
Schaffer et al., 2004[47] NA	Pharmacy adherence % (days of medication dispensed (number of doses dispensed divided by daily dosage), divided by the number of days between refill and date of study visit) for past 3 mo.	Baseline, 3, 6 mo; 3 month time frame	PRD	G1: 11 G2: 10 G3:12 G4:13	% (SD) G1: Pre: 0.41 (0.42) 3 mo: 0.53 (0.41) 6 mo: 0.77 (0.24) G2: Pre: 0.32 (0.39) 3 mo: 0.40 (0.32) 6 mo: 0.48 (0.38) G3: Pre: 0.62 (0.34) 3 mo: 0.73 (0.23) 6 mo: 0.77 (0.24) G4 : Pre: 0.62 (0.40) 3 mo: 0.42 (0.39) 6 mo: 0.40 (0.44) BL-3 mo: G4 vs. G2 p = .4 G4 vs. G3 p = .02* G4 vs. G1 p = .07 Pre-6 mo: G4 vs. G2 p = .17 G4 vs. G3 p = .02* G4 vs. G1 p = .04*
Schectman et al., 1994[48] NA	Answer at 2 months to interview question: "During the past week, how many doses of your medication have you missed?"	7 day timeframe; 3 times total every 2 months	Self-report	**Niacin**: G1: 40 G2: 40 **BAS**: G1: 18 G2: 22	**Niacin**: G1: 76 +/-5 G2: 77 +/- 6 95% CI, NR p: 0.85 **BAS**: G1: 76 +/- 7 G2: 60 +/- 9 95% CI, NR p: 0.14

Author, Year Trial Name	Medication Adherence Outcome 1	Description of Timing of Measurement of Adherence Outcome 1	Data Source	N	Results
Schneider et al., 2008[49] NA	Percentage of patients who had prescriptions refilled on time (±5 days of due date)	Calculated for all previous months at 6 month and 12 month follow-ups	PRD	G1: 47 G2: 38	Mean (SD) G1: 80.4 (21.2) G2: 66.1 (28.0) 95% CI, NR p: 0.12
Schnipper et al., 2006[50] NA	Medication adherence score on previous day	Whether patient took each medication exactly as prescribed on previous day	Self-report	G1: 92 G2: 84	0-100, 100 represents complete adherence with all medications G1: 88.9 (0.71-1.00) G2: 87.5 (0.73-1.00) 95% CI, NR p: 0.91
Simon et al., 2006[51] na	Filled prescriptions for at least 90 days of continuous antidepressant treatment at a minimally adequate dose	Measured once at 6 months	PRD	G1: 98 G2: 97	G1: 63 (64%) G2: 53 (55%) Chi-squared: 1.88 p: .17
Sledge et al., 2006[52] NA	Medication adherence score	NR	Self-report	G1: NR G2: NR	G1: NR G2: NR 95% CI, NR p: NR, text states that there was no significant difference between groups
Smith et al., 2008[53] NR	Absolute increase in proportion of days covered per month for the entire follow-up period of 9 mos.	last 30 days; 9 times; 1 month apart	PRD	G1: 426 G2: 410	G1: 4.3% mean absolute increase in days covered per month compared to G2 p= 0.04
Solomon et al., 1998[54] na Gourley et al., 1998[55] NA	Self-report of compliance comparing Visit 1 and Visit 5 in HTN group	Visit 1: baseline Visit 5: between 4 and 6 months	Self-report	G1: 62 G2: 70	G1: Visit 1: 0.63 (SD 0.111) Visit 5: 0.23 (SD 0.054) CI: NR p <0.05 G2: Visit 1: 0.60 (0.87) Visit 5: 0.61 (0.94) 95% CI NR p NR

Author, Year Trial Name	Medication Adherence Outcome 1	Description of Timing of Measurement of Adherence Outcome 1	Data Source	N	Results
Stacy et al., 2009[56] NA	6 month point prevalence persistency: subject being in possession of a statin at the end of the 180-day observation period	6 months from baseline; 1 time; NA	PRD	G1: 253 G2: 244	G1: 70.4% G2: 60.7% Unadjusted OR (90% CI): 1.54 (1.13-2.10) Adjusted OR (90%CI): 1.64 (1.19-2.26) p: <0.05
Taylor et al., 2003[57] NA	Compliance	At 12 months: Took ≥80% of all medications in past month (number of self-reported missed doses in past month of each med were divided by total prescribed doses for that month; %s for all meds were averaged together)	Self-report	G1: 33 G2: 36	Mean (SD) compliant patients G1: 100 G2: 88.9 (6.3) 95% CI, NR p: 0.115
Vivian et al., 2002[58] NA	Compliance survey at 6 months: how often do you forget to take your medication (forgets>=once/wk)? (%)	Varied b/t groups; compliance measured in G1 at monthly visits, only measured at baseline and study end for G2	Self-report	G1: 26 G2: 27	G1: 68% G2: 48% 95% CI, NR p: 0.252
Waalen et al., 2009[59] NA	Percentage of women using osteoporosis medication	Measured at 1 year and 30 days from entry into study using pharmacy database	PRD	G1: 109 G2: 102	G1: 68.8% filled rx G2: 45.1% filled rx 95% CI, NR p: <0.001
Wakefield et al., 2011[60] NA	Adherence [measured by 2 scales: Self-Reported Medication Taking Scale for HTN and DM validated regimen adherence scale addressing medication, diet, exercise, and BG testing]	12 months; 1 time; NA	Self-report	G1: NR G2: NR G3: NR	G1: NR G2: NR G3: NR 95% CI,NR p: NR Adherence improved in all 3 groups but no signifcant difference between groups
Weinberger et al., 2002[61] NA	Single item indicator for proportion of noncompliance (Inui et al.) - adjusted OR at 12 months comparing 1)Pharm Care to peak flow monitoring and 2) Pharm care vs. Usual care	Assessed at baseline, 6 and 12 months; time frame is previous 2 months	Self-report	Overall N: 898 G1: 356 G2: 296 G3: 246	Pharm Care vs. Peak Flow monitoring (G1 vs. G2): aOR: 0.81 (0.58-1.12) Pharm Care vs. Usual Care (G1 vs. G3): aOR: 1.09 (0.80-1.49)

Author, Year Trial Name	Medication Adherence Outcome 1	Description of Timing of Measurement of Adherence Outcome 1	Data Source	N	Results
Weymiller et al., 2007[62] Statin Choice Randomized Trial Jones et al., 2009[63] Statin Choice Randomized Trial	Post-intervention adherence (i.e., not missing any doses) in the last week	Measured once at 3 months after the intervention; measured only among those taking statins;	Self-report	G1: 33 G2: 29	G1: 31 G2: 23 Odds ratio: 3.4 95% CI, 1.5-7.5 p: NR <<*Note: article reports number of people in each group who missed 1 or more doses in the last week, the numbers above are the people who did not miss a dose, i.e. those who were adherent*>>
Williams et al., 2010[64] NA	Percent adherence to ICS at end of study; all adherence measures constructed as follows: linked electronic prescription information with fill information from pharmacy claims data to estimate the number of days that a given fill of an ICS would last (i.e., days supplied). This was calculated by dividing the canister size (i.e., puffs per canister) as derived from National Drug Codes in pharmacy claims by the dosage information (i.e., puffs per day). The calculated days of supply was then used to estimate adherence as a continuous measure of medication availability equal to the cumulative days of supply divided by the number of days of observation. This estimates the proportion of time that the patients took their medication.	Once, end of study, measured for past 3 months of intervention	Other	G1: 1335 G2: 1363	Mean +/- SE: G1: 21.3 +/- 2.5 G2: 23.3 +/- 2.2 95% CI, NR p: .553

Author, Year Trial Name	Medication Adherence Outcome 1	Description of Timing of Measurement of Adherence Outcome 1	Data Source	N	Results
Wilson et al., 2010[65] Better Outcomes of Asthma Treatment (BOAT)	Medication acquisition at Year 1 - all asthma meds; Fill/refill adherence was measured using a continuousmedication acquisition (CMA) index for each year, calculated as the total days' supply acquired in a given year divided by 365 days	Follow-up year 1, continuous measure for entire year	PRD	G1: 204 G2: 204 G3: 204	G1: 0.67 G3: 0.46; p: 0.0001 Group difference: 0.21 95% CI, 0.13-0.28 G1: 0.67 G2: 0.59; p: .0029 Group difference: 0.08 95% CI, 0.01-0.15 G2: 0.59 G3: 0.46 p: .0008 Group difference: 0.13 95% CI, 0.05-0.20
Wolever et al., 2010[66] NA	Morisky Adherence Scale	6 months	Self-report	G1: 27 G2: 22	G1: Pre (Mean, SD) = 6.7 (0.96), Post (Mean, SD) = 7.2 (0.97) Change Over Time (P) = 0.004 G2: Pre (Mean, SD) = 6.7 (1.25), Post (Mean, SD) = 6.9 (1.25) Change Over Time (P) = NS 95% CI, NR p: NR

Author, Year Trial Name	Medication Adherence Outcome 1	Description of Timing of Measurement of Adherence Outcome 1	Data Source	N	Results
Zhang et al., 2010[67] (cont'd) NA	Medication Possession Ratio	Pre and post Part D	Other	**Hyperlipidemia** G1: 418 G2: 647 G3: 5093 G4: 3027 **Diabetes** G1: 247 G2: 304 G3: 2214 G4: 1253 **Hypertension:** G1: 980 G2: 1234 G3: 8380 G4: 4141A	**Hypertension** Unadjusted G1 Pre: 62.4; Post: 75.2 G2 Pre: 81.1; Post: 82.6 G3 Pre: 82.7; Post: 83.7 G4 Pre: 85.1; Post: 84.0 Multivariate 2-year Part D Effect, estimate (95% CI) G1: 13.5 (18.6,25.0) G2: 2.6 (1.2, 4.1) G3: 2.5 (1.7, 3.2) G4 Ref % Change, Estimated Effects/pre Value (95% CI) G1: 21.8 (18.6, 25.0) G2: 3.2 (1.5, 5.0) G3: 3.0 (2.0, 3.9)

Author, Year Trial Name	Medication Adherence Outcome 1	Description of Timing of Measurement of Adherence Outcome 1	Data Source	N	Results
Zhang et al., 2010[67] NA (Cont'd)	See above	See Above	See Above	See Above	**Hyperlipidemia** Unadjusted G1 Pre: 47.3; Post: 59.9 G2 Pre: 57.6; Post: 63.3 G3 Pre: 62.3; Post: 65.1 G4 Pre: 74.4; Post: 73.0 Multivariate 2-year Part D Effect, estimate (95% CI) G1: 13.4 (10.1, 16.8) G2: 7.3 (4.8, 9.8) G3: 4.4 (3.3, 5.6) G4 Ref % Change, Estimated Effects/pre Value (95% CI) G1: 28.5 (21.4, 35.8) G2: 12.6 (8.3, 17.0) G3: 7.1 (5.3, 9.1) **Diabetes** (Unadjusted) G1 Pre: 57; Post: 69.6 G2 Pre: 77.3; Post: 76.2 G3 Pre: 75.4; Post: 73.3 G4 Pre: 81.8; Post: 78.2 Multivariate 2-year Part D Effect, estimate (95% CI) G1: 17.9 (13.7, 22.1) G2: 4.5 (1.0, 7.9) G3: 3.6 (1.8, 5.3) G4 Ref % Change, Estimated Effects/pre Value (95% CI) G1: 31.4 (24.0, 38.8) G2: 5.8 (1.3, 10.3) G3: 4.8 (2.4, 7.1)

Table D10. Medication adherence outcomes 2

Author, Year Trial Name	Medication Adherence Outcome 2	Description of Timing of Measurement of Adherence Outcome 2	Data Source	N	Results
Bogner et al., 2008[4] NA	Hypertension adherence: % of prescribed doses taken; calculated as number of doses taken divided by the number of doses prescribed during the observation period multiplied by 100%. Dichotomized with 80% threshold	Measured over 6 week study period for entire study period	MEMS	G1: 32 G2: 32	G1: 25 (78.1) G2: 10 (31.3) 95% CI, p: <.001
Bogner et al., 2010[5] NA	>80% adherence to an antidepressant	4 times, biweekly beginning at baseline and ending at week 6	MEMS	G1: 29 G2: 29	**BL** G1: 8 (27.6%) G2: 4 (13.8%) 95% CI, NR p: 0.17 **EP at 6 weeks** G1: 18 (62.1%) G2: 3 (10.3%) 95% CI, NR p: <0.001
Bosworth et al., 2005[6] V-STITCH	Adherence at 6 months among those adherent at baseline	last 6 months; 2 times (including baseline); 6 months	Self-report	Total: 387 G1: NR G2: NR	G1: 83% G2: 85% 95% CI, NR p: 0.68
Capoccia et al., 2004[9] na	Adherence to antidepressants - at 6 mo	Defined as use of antidepressants for at least 25 of the past 30 days; measured at 3, 6, 9, 12 mos	Self-report	G1: NR G2: NR	G1: 78% G2: 73% 95% CI, NR NS

Author, Year Trial Name	Medication Adherence Outcome 2	Description of Timing of Measurement of Adherence Outcome 2	Data Source	N	Results
Choudhry et al., 2010[12] NA	Odds of being fully adherent (monthly)	Measured monthly over the 24-month study period	Other	Overall N: 52,631 G1: 2051 G2: 779 G3: 38,174 G4: 11,627	Statin users Adjusted for comorbidity & demographics: G1: 17.0% increase over G3, with no subsequent change in slope 95% CI, NR p: <0.05 Matched by first fill date for eligible prescription in study timeframeG1: 15.1% increase over G3, with no subsequent change in slope 95% CI, NR p: <0.05 Clopidogrel users Adjusted for comorbidity & demographics: G2: 19.9% increase over G4, with no subsequent change in slope 95% CI, NR p: < 0.05 Matched by first fill date for eligible prescription in study timeframe G2: 33.9% increase over G4, with no subsequent change in slope 95% CI, NR p< 0.05

Author, Year Trial Name	Medication Adherence Outcome 2	Description of Timing of Measurement of Adherence Outcome 2	Data Source	N	Results
Choudhry et al., 2011[13]	Full adherence (among all patients)	Having a supply of medications available on at least 80% of days during follow-up. Patients who lost eligibility before randomization or who did not fill a prescription after randomization were considered to be nonadherent.	Prescription claims records	G1: 2845 G2: 3010	**All 3 medication classes** G1: 12.1 G2: 8.9 OR (95% CI): 1.41 (1.18-1.67) p: <0.001 **ACE inhibitor or ARB** G1: 27.7 G2: 22.9 95% CI, NR OR (95% CI): 1.31 (1.14-1.49) p: <0.001 **Beta-blocker** G1: 30.7 G2: 25.2 95% CI, NR OR (95% CI): 1.32 (1.16-1.49) p: <0.001 **Statin** G1: 38.6 G2: 31.6 95% CI, NR OR (95% CI): 1.37 (1.20-1.56) p: <0.001
Friedman et al., 1996[14] NA	Change in Antihypertensive medication adherence for baseline nonadherent subjects (Proportion of total number of doses taken divided by the number that should have been taken by each subject)	Change scores were computed using value at 6 months minus value at baseline	Pill count	Overall N: 26 G1: NR G2: NR	G1: 36.0% G2: 26.0% 95% CI, NR p: 0.03
Guthrie et al., 2001[17] First Myocardial Infarction (MI) Risk Reduction Program	Medication compliance survey: missed no doses in past 7 days, %	7 days; 2 times; 3 months	Self-report	G1: 3635 G2: 913	At 6 months G1: 64.3 G2: 61.8 95% CI, NR p: NR

Author, Year Trial Name	Medication Adherence Outcome 2	Description of Timing of Measurement of Adherence Outcome 2	Data Source	N	Results
Hoffman et al., 2003[18] NA	Percent adherence using medication possession ratios, at 3 months	Measured once at 3 months for previous 30 days; adherence defined as < 10 gap days in 30-day period	PRD	G1: 4899 G2: 4665	G1: 66.9 G2: 66.5 95% CI, NR p: < 0.01
Hunt et al., 2008[19] NA	Increase in adherence from baseline to final assessment	At baseline and at end point	Self-report	G1: 142 G2: 130	G1: 61% at BL, 67% at end point, p=0.08 G2: no significant increase from BL to final (p= 0.52) [BL and EP % not reported] 95% CI, NR p: NR
Janson et al., 2009[21] NA	The odds of maintaining greater than 60% adherence -the OR represents a comparison of T2 vs. T1 within groups; however, I report the p-value for the between-groups comparison	Measured biweekly during 4-week intervention (T0-T1); measured at 4-week intervals for following 14 weeks of observation (T1-T2)	Other	NR	**T0-T1** G1: 9.2 G2: 0.4 p: 0.02 **T1-T2** G1: OR: 0.3 G2: OR: 1.1 p: .31
Janson et al., 2003[20] NA	ICS adherence (number of puffs recorded daily in the diary divided by the number of puffs prescribed) between group-difference in change from baseline to final visit (95% CI) Source of data was self-report supplemented by medication monitors	Assessed at baseline, and end of week 1, 2, 5, 7; time frame for baseline measurement was one week; time frame for final measurement not reported	Other	G1: 33 G2: 32	Between group difference: 24 (5 to 43), p= 0.01

Author, Year Trial Name	Medication Adherence Outcome 2	Description of Timing of Measurement of Adherence Outcome 2	Data Source	N	Results
Johnson et al., 2006[23] NR	Pre-action sample only - Reaching Action (A) or M (Maintenance) stage for adherence, %; Action defined as having improved adherence for < 6 months; Maintenance defined as having improved adherence for >6 months; [Data source: complete case analysis evaluating Stage of Change]	Last 6 months; 4 times every 6 months (0,6,12, and 18 months)	Self-report	G1: NR G2: NR	**BL** G1: in figure only G2: in figure only 95% CI, NR p:NR **6 months** G1: in figure only G2: 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

Author, Year Trial Name	Medication Adherence Outcome 2	Description of Timing of Measurement of Adherence Outcome 2	Data Source	N	Results
Johnson et al., 2006[22] NR	Pre-action sample only Medication Adherence Scale score [Data Source: 4-item scale assessing whether individual has engaged in various forms of non-adherence]	Last 3 months; 4 times; measured every 6 months (0,6,12, and 18 mos)	Self-report	**BL** Overall N: 262 G1: NR G2: NR **6 months** Overall N: 180 G1: NR G2: NR **12 months** Overall N: 163 G1: NR G2: NR **18 months** Overall N: 161 G1: NR G2: NR	**BL** G1: in figure only G2: in figure only OR: NR p:NR **6 months** G1: in figure only G2: in figure only OR=1.49 p<0.01 **12 months** G1: in figure only G2: in figure only OR=1.62 p<0.001 **18 months** G1: in figure only G2: in figure only OR=1.62 p<0.01
Katon et al., 1995[24] NA	% receiving adequate dosage of antidepressants for ≥90 days (details NR)	During continuation phase of treatment (3-7 months)	PRD	**Major depression group** N=91 **Minor depression group** N=126	**Major depression group** G1: 75.5 G2: 50.0 95% CI, p: <0.01 **Minor depression group** G1: 79.7 G2: 40.3 95% CI, p: <0.001
Katon et al., 1996[25] NA	Medication adherence - telephone interview asking if they were still taking antidepressants and considered adherent if they reported taking medication at least 25 out of last 30 days	Measured at 4-month follow up	Other	G1: 76 G2: NR	**Major Depression Group at 4-month follow up (% adherent)** G1: 89% G2: 62% p=0.02 **Minor Depression Group at 4-month follow up (% adherent)** G1: 74% G2: 44% p=.01

Author, Year Trial Name	Medication Adherence Outcome 2	Description of Timing of Measurement of Adherence Outcome 2	Data Source	N	Results
Katon et al., 1999[26] NA Katon et al., 2002[27] NA	Percent receiving adequate dosage of antidepressants for at least 90 days in previous 6 months, as indicated by AHCPR guidelines(Reported in 9123)	Likely measured once at 6-months for the previous 6 months of data	PRD	G1: 114 G2: 114	G1: 68.8% G2: 43.8% Chi-square: 12.60 p: 0.0001
Katon et al., 2001[28] NA Ludman et al., 2003[29] NA Van Korff et al., 2003[30] NA	Adequate dosage of antidepressant treatment	Measured at 3, 6, 9, 12 months	PRD	G1: NR G2: NR	Adjusted OR G1: G2, 2.08 95% CI, 1.41 to 3.06 p: < 0.001
Lee et al., 2006[31] FAME	>/=80% adherence to all medications, %	Last 2 months; 4 times (including baseline at 8 months); 2 months	Pill count	G1: 77 G2: 69	G1: 97.4 G2: 21.7 95% CI, NR p<0.001

Author, Year Trial Name	Medication Adherence Outcome 2	Description of Timing of Measurement of Adherence Outcome 2	Data Source	N	Results
Lin et al., 2006[32] NA	Adjusted mean difference in percentage of days nonadherent (baseline minus endpoint)	NA	PRD	Oral hypoglycemic agent **BL** G1: 103 G2: 103 **EP** G1: 103 G2: 103 ACE inhibitor **BL** G1: 54 G2: 65 **EP** G1: 59 G2: 52 Lipid-lowering agent **BL** G1: 50 G2: 52 **EP** G1: 54 G2: 63	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

Author, Year Trial Name	Medication Adherence Outcome 2	Description of Timing of Measurement of Adherence Outcome 2	Data Source	N	Results
Maciejewski et al., 2010[33]	Percent change in medication possession ratio (MPR) from baseline (adherence differences between G1 and G2) Matched analysis with covariates	24 monthly assessments: 12 in the pre-intervention period and 12 in the post-period	Other	Matched pairs, N in G1 and G2 identical for each medication. N's shown below are for each group **Metformin**: 2,201 **Diruetics:** 7,417 **ACE inhibitors**:6,379 **Beta-blockers**: 4,992 **Statins:** 7,757 **Calcium-channel blockers:** 3,209 **Angiotensin-receptor blockers:** 3,259 **Cholesterol absorption inhibitors:** 1,681	**Metformin**: 3.69% p: <0.001 **Diuretics**: 3.35% p: <0.001 **ACE inhibitors**: 3.10% p: <0.001 **Beta-blockers**: 2.69% p: <0.001 **Statins**: 2.56% p: <0.001 **Calcium-channel blockers**: 1.31% p: <0.05 **ARBS**: -0.02% p: NS **Cholesterol absorption inhibitors**: -0.80% p: NS
Mann et al., 2010[34] The Statin Choice	% of participants with good adherence at 6 months using Morisky	Same as mentioned for 3 months	Self-report	G1: NR G2: NR	G1: NR G2: NR 95% CI, p: No significant difference reported between groups for overall 80% with "good adherence" for whole group at 6 months
Montori et al., 2011[35]	Adherence: Median (range) proportion of days covered	Measured at 6 months	PRD	G1: 23 G2: 19	G1: 100 (86.1-100) G2: 98.2 (0-100) 95% CI, NR p: 0.09

Author, Year Trial Name	Medication Adherence Outcome 2	Description of Timing of Measurement of Adherence Outcome 2	Data Source	N	Results
Murray et al., 2007[36] NA	"Taking Adherence": % of prescribed medication doses taken based on physician's prescription	Post-intervention (3 additional mos - months 10-12) Frequency: continuous daily MEMS monitoringDuration between measures: 12 to 24 hours, depending on med frequency	MEMS	G1: 122 G2: 192	Proportion (95% CI) G1: 70.6% (64.9-76.2) G2: 66.7% (62.3-70.9) Difference 3.9% (-2.8-10.7) p=NR
Nietert et al., 2009[37] NA	Filled prescription for any qualified medication in the same chronic disease classification as the index medication, within 30 days of index date	NR	PRD	G1: 1018 G2: 1016 G3: 1014	Unadjusted G1: N (%) = 207 (20.3%) G2: N (%) = 213 (21.0%) G3: N (%) = 243 (24.0%) 95% CI, NR p: NR Adjusted G1: Hazard ratio (HR, 98.3% CI) = 0.79 (0.61-1.03) 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
Okeke et al., 2009[38] NA	Change in adherence rates (unadjusted)	Dosing aids were 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)	Other	G1: 35 G2: 31	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

Author, Year Trial Name	Medication Adherence Outcome 2	Description of Timing of Measurement of Adherence Outcome 2	Data Source	N	Results
Powell et al., 1995[40] NA	Compliance (MPR $\geq$ 0.80)	Refill data collected over a 9-month period	PRD	G1: 1993 G2: 2253	**Overall** (N (%)) G1: 917 (46%) G2:998 (44%) 95% CI, NR p: NR **Benazepril** (N (%)) G1: 78 (45%) G2: 104 (44%) 95% CI, NR p: NR **Transdermal estrogen** (N (%)) G1: 266 (37%) G2: 209 (35%) 95% CI, NR p: NR **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
Pyne et al., 2011[41] HIV Translating Initiatives for Depression Into Effective Solutions (HITIDES)	Antidepressant regimen adherence - at 12 months	Each measurement is percentage adherence over previous 4 days (i.e. total number of prescribed pills taken divided by total number of prescribed, transformed to dichotomous outcome with cutpoint at >=80%). 3 measurements taken: baseline, 6-month and 12-months.	Self-report	G1: 59 G2: 60	G1: 45/59 (76.3) G2: 51/60 (85.0) OR: 0.55 (0.21-1.44) Adjusted OR: 0.56 (0.20-1.57) Adjusted p: 0.27

Author, Year Trial Name	Medication Adherence Outcome 2	Description of Timing of Measurement of Adherence Outcome 2	Data Source	N	Results
Rich et al., 1996[42] NA	Overall compliance rates by method 2: percentage of pills taken correctly for all current medications (pooled) determined by pill count at home visit by pharmacist or trained pharmacy assistant	30 days +/- 2 days after discharge; 1 time; NA	Pill count	G1: 80 G2: 76	Overall: 84.3% +/- 15.0% G1: 87.5 +/- 12.6% G2: 80.9 +/- 16.7% 95% CI, NR p: 0.003
Rickles et al., 2005[43] NA	% omitted antidepressant doses at 6 months	2 measurements, each for 3 month time period	PRD	G1: 28 G2: 32	Without ITT: N (Mean ± SD) G1:28 (30.3 ± 36.4) G2: 32 (48.6 ± 39.2) p <0.05 (one tailed) With ITT, the difference was not significant (data NR)
Ross et al., 2004[44] NR	General adherence score (0-100 score)	NR; 3 times (including baseline); 6 months	Self-report	G1: NR G2: NR	**6 months** G1: 81 G2: 78 Difference (CI): +2.3 (-3.7 to 8.3) p: NR **12 months** G1: 85 G2: 78 Difference (CI): +6.4 (1.8 to 10.9) p: 0.01
Rudd et al., 2004[45] NA	Proportion of medications taken correctly among those on a once-daily dosing regimen	1 day; daily ; 6 months	MEMS	NR	G1: 82% (28%) G2: 75% (27%) 95% CI, NR p: NR, not significant per text
Rudd et al., 2009[46] NA	Percent Change at 6 months and 12 months in Medication Adherence Outcome	Measures at 6 months and 12 months; percent change from baseline to 6 months and percent change from base line to 12 months	Self-report	**BL** G1: 51 G2: 63 **6 mos** G1: 49 G2: 57 **12 mos** G1: 48 G2: 57	Percent Change (Scales show improvement with decreased scores) **BL to 6 months** G1: -4.76 G2: 0.25 95% CI, NR p: 0.33 **BL to 12 months** G1: -12.21 G2: -3.12 95% CI, NR p: 0.10

Author, Year Trial Name	Medication Adherence Outcome 2	Description of Timing of Measurement of Adherence Outcome 2	Data Source	N	Results
Schaffer et al., 2004[47] NA	Self-reported adherence: number of doses of preventive medication missed during the 2 weeks prior to each study visit.	Baseline, 3, 6 mo; 2 week timeframe	Self-report	G1: 11 G2: 10 G3:12 G4:13	Self-report missed: mean (SD) G1: Pre: 1.72 (2.15) 3 mo: 2.40 (3.10) 6 mo: 1.17 (1.53) G2: Pre: 8.10 (12.63) 3 mo: 7.70 (10.85) 6 mo: 4.68 (27.34) G3: Pre: 6.58 (9.52) 3 mo: 8.91 (15.25) 6 mo: 1.17 (1.53) G4 : Pre: 3.61 (7.65) 3 mo: 6.25 (10.49) 6 mo: 3.75 (7.89) Pre-3 mo G4 vs. G2 p = .9 G4 vs. G1 p = .7 G4 vs. G3 p = .5 Pre-6 mo G4 vs. G3 p = .2 G4 vs. G2 p = .2 G4 vs. G1 p = .5

Author, Year Trial Name	Medication Adherence Outcome 2	Description of Timing of Measurement of Adherence Outcome 2	Data Source	N	Results
Schectman et al., 1994[48] NA	Prescription refill proportion at 2 months	Monthly timeframe; measured 2 times; 1 month between measures	PRD	**Niacin**: G1: 40 G2: 40 **BAS**: G1: 18 G2: 22	**Niacin**: G1: 90 +/- 2 G2: 84 +/- 3 95% CI, NR p: 0.07 **BAS**: G1: 88 +/-4 G2: 82 +/- 4 95% CI, NR p: 0.32
Schneider et al., 2008[49] NA	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 1st and last rx dispensing)	Calculated for all previous months at 6 month and 12 month follow-ups	PRD	G1: 47 G2: 38	Mean (SD) G1: 0.93 (11.4) G2: 0.87 (14.2) 95% CI, p: 0.039
Schnipper et al., 2006[50] NA	#/% of patients non-adherent with at least 1 medication	NR	Self-report	G1: 67 G2: 62	G1: 36 (54%) G2: 33 (53%) 95% CI, p: >0.99
Smith et al., 2008[53] NR	Likelihood of having at least 80% proportion of days covered across all 9 months of follow-up	last 30 days; 9 times; 1 month apart	PRD	G1: 426 G2: 410	G1: 64.8% G2: 58.5% RR: 1.17 95% CI, 1.02-1.29
Solomon et al., 1998[54] na Gourley et al., 1998[55] NA	Self-report of compliance comparing Visit 1 between Intervention and Control group in HTN group	At baseline	Self-report	G1: 62 G2: 70	G1: 0.60 (0.087) G2: 0.63 (0.111) 95% CI, NR p: 0.75
Stacy et al., 2009[56] NA	Continuous Persistence: having any statin prescription dispensed at least every 30 days after the end date of a previous prescription for a statin	6 months from baseline; 1 time; NA	PRD	G1: 253 G2: 244	G1: 52.2% G2: 44.3% Unadjusted OR (90% CI): 1.37 (1.02-1.85) Adjusted OR (90%CI): 1.41 (1.05-1.94) p: <0.10

Author, Year Trial Name	Medication Adherence Outcome 2	Description of Timing of Measurement of Adherence Outcome 2	Data Source	N	Results
Vivian et al., 2002[58] NA	Compliance survey at 6 months: How often do you stop taking your medication when you are feeling better? (>=once/wk)	Varied b/t groups; compliance measured in G1 at monthly visits, only measured at baseline and study end for G2	Self-report	G1: 26 G2: 27	G1: 32% G2: 20% 95% CI, NR p: 0.520
Weinberger et al., 2002[61] NA	Morisky 4-item scale range from 0 (low) to 4 (high) - 12 month outcome	Assessed at baseline, 6 and 12 months; time frame is previous 2 months	Self-report	Overall N: 898 G1: 356 G2: 296 G3: 246	G1: 0.87 (0.05) G2: 0.85 (0.05) G3: 0.92 (0.06) p=0.57
Weymiller et al., 2007[62] Statin Choice Randomized Trial Jones et al., 2009[63] Statin Choice Randomized Trial	Post intervention adherence at 3 months (Adherence stratified by mode of delivery)	Not missing any doses in the past week	Self-report	NS	There were no statistically significant effects of mode of delivery on adherence to statins at 3 months (OR 0.8, CI 0.3, 2.6).
Wilson et al., 2010[65] Better Outcomes of Asthma Treatment (BOAT)	Medication acquisition - ICS; Fill/refill adherence was measured using a continuousmedication acquisition (CMA) index for each year, calculated as the total days' supply acquired in a given year divided by 365 days	Follow-up year 1, continuous measure for entire year	PRD	G1: NR G2: NR G3: NR	G1: 0.59 G3: 0.37; p: 0.0001 G1: 0.59 G2: 0.52; p: .017 G2: 0.52 G3: 0.37 p: .0001

Author, Year Trial Name	Medication Adherence Outcome 2	Description of Timing of Measurement of Adherence Outcome 2	Data Source	N	Results
Zhang et al., 2010[67] NA	Medication Possession Ratio ≥0.80 (likelihood of being adherent)	Pre and post Part D	Other	**Hyperlipidemia** G1: 418 G2: 647 G3: 5093 G4: 3027 **Diabetes** G1: 247 G2: 304 G3: 2214 G4: 1253 **Hypertension**: G1: 980 G2: 1234 G3: 8380 G4: 4141	**Hyperlipidemia** Unadjusted G1 Pre: 27.5; Post: 43.9 G2 Pre: 39.2; Post: 48.2 G3 Pre: 42.1; Post: 49.3 G4 Pre: 57.4; Post: 61.3 Multivariate 2-Year Part D Effect, estimate (95% CI) G1: 1.67 (1.35, 2.07) G2: 1.22 (1.04, 1.43) G3: 1.14 (1.06, 1.24) G4: 1.00 **Diabetes** Unadjusted G1 Pre: 39.7; Post: 57.2 G2 Pre: 68.0; Post: 67.1 G3 Pre: 62.0; Post: 61.9 G4 Pre: 70.6; Post 66.6 Multivariate 2-Year Part D Effect, estimate (95% CI) G1: 2.36 (1.81, 3.08) G2: 1.17 (0.9, 1.51) G3: 1.21 (1.06, 1.39) G4: 1.00 **Hypertension** Unadjusted G1 Pre: 47; Post: 66.6 G2 Pre: 73.3; Post: 76.6 G3 Pre: 74.9; Post: 77.4 G4 Pre: 78.4; Post: 78.5 Multivariate 2-Year Part D Effect, estimate (95% CI G1: 2.09 (1.82, 2.40) G2: 1.13 (0.99, 1.29) G3: 1.14 (1.05, 1.23) G4: 1.00

Table D11. Medication adherence outcomes 3

Author, Year Trial Name	Medication Adherence Outcome 3	Description of Timing of Measurement of Adherence Outcome 3	Data Source	N	Results
Bosworth et al., 2005[6] V-STITCH	Adherence at 6 months among those non-adherent at baseline	Last 6 months; 2 times (including baseline); 6 months	Self-report	Total: 200 G1: NR G2: NR	G1: 46% G2: 34% 95% CI, NR p: 0.08
Capoccia et al., 2004[9] NA	Adherence to antidepressants - at 9 mo	Defined as use of antidepressants for at least 25 of the past 30 days; measured at 3, 6, 9, 12 mos	Self-report	G1: NR G2: NR	G1: 48% G2: 67% 95% CI, NR p: NS
Choudhry et al., 2011[13] MI FREEE	Mean medication possession ratio (among patients who filled at least 1 prescription)	Number of days for which patients had a supply of each medication class available divided by the # days they were eligible for that medication.	Prescription claims data	**All 3 medication classes** G1: 1385 G2: 1389 **ACE inhibitor or** ARB G1: 1759 G2: 1775 **Beta-blockers** G1: 2159 G2: 2224 **Statins** G1: 2223 G2: 2267	**All 3 medication classes** G1: 67.4 (15.5) G2: 62.9 (26.3) Absolute difference (95% CI): 4.5 (2.5-6.4) p: <0.001 **ACE inhibitor or ARB** G1: 66.5 (29.6) G2: 60.8 (30.7) Absolute difference (95% CI): 5.8 (3.6-8.1) p: <0.001 **Beta-blocker** G1: 65.0 (28.9) G2: 61.0 (28.9) Absolute difference (95% CI): 4.0 (2.1-5.9) p: <0.001 **Statin** G1: 70.5 (27.0) G2: 65.0 (28.4) Absolute difference (95% CI): 5.5 (3.6-7.5) p: <0.001

Author, Year Trial Name	Medication Adherence Outcome 3	Description of Timing of Measurement of Adherence Outcome 3	Data Source	N	Results
Friedman et al., 1996[14] NA	Change in Antihypertensive medication adherence for baseline adherent subjects (Proportion of total number of doses taken divided by the number that should have been taken by each subject)	Change scores were computed using value at 6 months minus value at baseline	Pill count	Overall N: 267 G1: NR G2: NR	G1: 0.6% G2: 3.0% 95% CI, NR p: 0.69
Hoffman et al., 2003[18] NA	Percent adherence using HEDIS guidelines, at 3 months	Measured once at 3 months; adherence defined as a total of 30 gap days since beginning treatment (days 1-84)	PRD	G1: 4899 G2: 4665	G1: 59.6 G2: 56.6 95% CI, NR p: < 0.01
Katon et al., 1996[25] NA	Medication adherence - telephone interview asking if they were still taking antidepressants and considered adherent if they reported taking medication at least 25 out of last 30 days	Measured at 1-, 4-, and 7-month follow up	Other	G1: 76 G2: NS	**Major Depression Group at 7-month follow up** (% adherent) G1: 79% G2: 54% p=0.07 **Minor Depression Group at 1-, 4-, and 7-month follow up** (% adherent) G1: 65% G2: 41% p=.04
Katon et al., 1999[26] NA Katon et al., 2002[27] NA	Percent receiving twice the dosage of the lower-range AHCPR guideline of antidepressant (Reported in 9123)	Likely measured once at 6-months for the previous 6 months of data	PRD	G1: 114 G2: 114	G1: 46.8% G2: 25.7% Chi-square: 9.36 p: 0.002
Montori et al., 2011[35] NA	Persistence: Median (range) number of days covered	Measured at 6 months	PRD	G1: 23 G2: 19	G1: 170 (30-180) G2: 180 (28-180) 95% CI, NR p: 0.38

Author, Year Trial Name	Medication Adherence Outcome 3	Description of Timing of Measurement of Adherence Outcome 3	Data Source	N	Results
Murray et al., 2007[36] NA	"Scheduling Adherence": Measure of adherence to timing, lower with day-to-day deviation in the timing of medication administration; daily meds need to be taken within 2.4 hrs of dose from preceding day; 2x/day meds need to be taken within 1.2 hrs of prior dose	During Intervention period (9 mos) Frequency: continuous daily MEMS monitoring Duration between measures: 12 to 24 hours, depending on med frequency	MEMS	G1: 122 G2: 192	(95% CI) G1: 53.1% (49.1-57.1) G2: 47.2% (43.4-50.9) Difference: 5.9% (0.4-11.5) p: NR
Nietert et al., 2009[37] NA	Filled prescription for any qualified medication in the same chronic disease classification as the index medication, within 60 days of index date	NR	PRD	G1: 1018 G2: 1016 G3: 1014	<u>Unadjusted</u> G1: N (%) = 348 (34.2%) G2: N (%) = 342 (33.7%) G3: N (%) = 373 (36.8%) 95% CI, NR p: NR <u>Adjusted</u> 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
Okeke et al., 2009[38] N-A	Change in adherence rates (adjusted)	Dosing aids were 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)	Other	G1: 34 G2: 28	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

Author, Year Trial Name	Medication Adherence Outcome 3	Description of Timing of Measurement of Adherence Outcome 3	Data Source	N	Results
Pyne et al., 2011[41] HIV Translating Initiatives for Depression Into Effective Solutions (HITIDES)	HIV medication regiment adherence - at 6 months	Each measurement is percentage adherence over previous 4 days (i.e. total number of prescribed pills taken divided by total number of prescribed, transformed to dichotomous outcome with cutpoint at >=95%). 3 measurements taken: baseline, 6-month and 12-months.	Self-report	G1: 96 G2: 98	G1: 74/96 (77.1) G2: 72/98 (73.5) OR: 1.23 (0.63-2.40) ; adjusted OR: 1.20 (0.60-2.31) Adjusted p: 0.65
Rich et al., 1996[42] NA	≥80% compliance by method 1	30 days +/- 2 days after discharge; 1 time; NA	Pill count	G1: 80 G2: 76	Overall: 121 pts (77.6%) G1: 68/80 (85.0%) G2: 53/76 (69.7%) 95% CI, NR p: 0.036
Rudd et al., 2004[45] NA	Proportion of medications taken correctly among those on a >=2 times-daily dosing regimen	1 day; daily ; 6 months	MEMS	NR	G1: 69% (34%) G2: 49% (41%) 95% CI, NR p: NR, not significant per text

Author, Year Trial Name	Medication Adherence Outcome 3	Description of Timing of Measurement of Adherence Outcome 3	Data Source	N	Results
Smith et al., 2008[53] NR	Proportion with a gap (in months) in filling beta blocker prescription	1 month, NR, 1 month	Refill data	**1 month gap**: G1:104 G2: 110 **2 month gap** G1:63 G2: 67 **3 month gap** G1: 43 G2: 51 **4 month gap** G1: 30 G2: 37	**1 month gap:** G1: 23% G2: 25% HR 0.85 (0.65, 1.12) adj HR 0.89 (0.67, 1.19) **2 month gap** G1: 14% G2: 15% HR 0.86 (0.61, 1.22) adj HR 0.95 (0.67, 1.33) **3 month gap** G1: 9% G2: 12% HR 0.77 (0.51, 1.16) adj HR 0.87 (0.60, 126) **4 month gap** G1: 7% G2: 9% HR 0.74 (0.46, 1.20) adj HR 0.85 (0.54, 1.35)
Solomon et al., 1998[54] na Gourley et al., 1998[55] NA	Self-report of compliance comparing Visit 1 and Visit 5 in HTN group	Visit 1: baseline Visit 5: between 4 and 6 months	Self-report	G1: 62 G2: 70	G1: Visit 1: 0.63 (SD 0.111) Visit 5: 0.23 (SD 0.054) CI: NR p <0.05 G2: Visit 1: 0.60 (0.87) Visit 5: 0.61 (0.94) 95% CI NR p NR

Author, Year Trial Name	Medication Adherence Outcome 3	Description of Timing of Measurement of Adherence Outcome 3	Data Source	N	Results
Stacy et al., 2009[56] NA	Medication possession ratio =/>80%	6 months from baseline; 1 time; NA	PRD	G1: 253 G2: 244	G1: 47.0% G2: 38.9% Unadjusted OR (90% CI): 1.39 (1.03 to 1.88) Adjusted OR (90%CI): 1.43 (1.05 to 1.96) p: <0.10
Vivian et al., 2002[58] NA	Compliance survey at 6 months: How often do you stop taking your medication when you think it is making you feel worse? (>/=once/wk)	Varied b/t groups; compliance measured in G1 at monthly visits, only measured at baseline and study end for G2	Self-report	G1: 26 G2: 27	G1: 40% G2: 20% 95% CI, NR p: 0.217
Wilson et al., 2010[65] Better Outcomes of Asthma Treatment (BOAT)	Medication acquisition at Year 2 - all meds; Fill/refill adherence was measured using a continuous medication acquisition (CMA) index for each year, calculated as the total days' supply acquired in a given year divided by 365 days	Measured at Year-2 follow-up as aggregate for entire year	PRD	G1: 204 G2: 204 G3: 204	Group differences G1-G3: 0.03 95% CI, -0.05 to 0.11 G1-G2: 0.04 95% CI, -0.04 to 0.12 G2-G3: -0.01 95% CI, -0.09 to 0.07 no significant differences across groups for all meds. No significant differences across groups for ICS alone, either.

Author, Year Trial Name	Medication Adherence Outcome 3	Description of Timing of Measurement of Adherence Outcome 3	Data Source	N	Results
Zhang et al., 2010[67] NA	Treatment intensity (average count of pills per day of treatment)	Pre and post part D	Other	**Hyperlipidemia** G1: 418 G2: 647 G3: 5093 G4: 3027 **Diabetes** G1: 247 G2: 304 G3: 2214 G4: 1253 **Hypertension:** G1: 980 G2: 1234 G3: 8380 G4: 4141	**Diabetes** <u>Unadjusted</u>) G1 Pre: 0.98; Post: 1.16 G2 Pre: 1.12; Post: 1.26 G3 Pre: 1.11 Post: 1.18 G4 Pre: 1.29; Post: 1.34 <u>Multivariate 2-Year Part D Effect, estimate (95% CI)</u> 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: <u>% change, estimated effects/pre value (95% CI)</u> G1: 18.8 (10.4 to 27.2) G2: 8.5 (2.50 to 14.4) G3: 1.8 (-1.2 to 4.8) G4: **Hypertension** <u>Unadjusted</u> G1 Pre: 1.26; Post: 1.56 G2 Pre: 1.48; Post: 1.63 G3 Pre: 1.52 Post: 1.64 G4 Pre: 1.65; Post: 1.75 <u>Multivariate 2-Year Part D Effect, estimate (95% CI)</u> 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: <u>% change, estimated effects/pre value (95% CI)</u> G1: 17.6 (13.0 to 22.1) G2: 3.7 (1.1 to 6.2) G3: 1.8 (0.4 to 3.3) G4:

Table D12. Medication adherence outcomes 4

Author, Year Trial Name	Medication Adherence Outcome 4	Description of Timing of Measurement of Adherence Outcome 4	Data Source	N	Results
Capoccia et al., 2004[9] NA	Adherence to antidepressants - at 12 mo	Defined as use of antidepressants for at least 25 of the past 30 days; measured at 3, 6, 9, 12 mos	Self-report	G1: 37 G2: 30	G1: 59% G2: 57% 95% CI, NR p: NS
Choudhry et al., 2011[13] MI FREEE	Full adherence (among patients who filled at least 1 prescription)	Having a supply of medications available on at least 80% of days during follow-up.	Prescription claims data	**All 3 medication classes** G1: 1385 G2: 1389 **ACE inhibitor** or ARB G1: 1759 G2: 1775 **Beta-blockers** G1: 2159 G2: 2224 **Statins** G1: 2223 G2: 2267	**All 3 medication classes** G1: 24.8 G2: 19.3 OR (95% CI): 1.36 (1.12 to 1.65) p: 0.002 **ACE inhibitor or ARB** G1: 44.9 G2: 38.8 OR (95% CI): 1.28 (1.10 to 1.49) p: 0.002 **Beta-blocker** G1: 40.4 G2: 34.1 OR (95% CI): 1.31 (1.14 to 1.50) p: <0.001 **Statin** G1: 49.3 G2: 41.9 OR (95% CI): 1.36 (1.18 to 1.56) p: <0.001
Hoffman et al., 2003[18] NA	Percent adherence using medication possession ratios, at 6 months	Measured once at 6 months for previous 30 days; adherence defined as < 10 days in 30-day period	PRD	G1: 4899 G2: 4665	G1: 52.3 G2: 50.2 95% CI, NR p: <0.001

Author, Year Trial Name	Medication Adherence Outcome 4	Description of Timing of Measurement of Adherence Outcome 4	Data Source	N	Results
Katon et al., 1996[25] NA	Adequate dosage	A dosage of antidepressant medication for at least 30 days at or above lowest dosage recommended by AHCPR guidelines	PRD	G1: 76 G2: NS	**Major Depression Group, for at least 30 days** (% adherent) G1: 66.7% G2: 57.6% p<.46 **Minor Depression Group, for at least 30 days** (% adherent) G1: 84.8% G2: 53.9% to <0.002
Montori et al., 2011[35] NA	Adherence: did not miss a dose	Asked at 6 months: "Have you missed any of your pills in the past week?"	Self-report	G1: 17 G2: 19	G1: 65% G2: 63% 95% CI, NR p: 0.92
Murray et al., 2007[36] NA	"Scheduling Adherence": Measure of adherence to timing, lower with day-to-day deviation in the timing of medication administration; daily meds need to be taken within 2.4 hrs of dose from preceding day; 2x/day meds need to be taken within 1.2 hrs of prior dose	Post-intervention (3 additional mos - months 10-12) Frequency: continuous daily MEMS monitoring Duration between measures: 12 to 24 hours, depending on med frequency	MEMS	G1: 122 G2: 192	(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
Nietert et al., 2009[37] NA	Filled prescription for any medication, within 30 days of index date	NR	PRD	G1: 1018 G2: 1016 G3: 1014	<u>Unadjusted</u> G1: N (%) = 460 (45.2%) G2: N (%) = 484 (47.6%) G3: N (%) = 490 (48.3%) 95% CI, NR p: NR <u>Adjusted</u> 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

Author, Year Trial Name	Medication Adherence Outcome 4	Description of Timing of Measurement of Adherence Outcome 4	Data Source	N	Results
Pyne et al., 2011[41] HIV Translating Initiatives for Depression Into Effective Solutions (HITIDES)	HIV medication regiment adherence - at 12 months	Each measurement is percentage adherence over previous 4 days (i.e. total number of prescribed pills taken divided by total number of prescribed, transformed to dichotomous outcome with cutpoint at >=95%). 3 measurements taken: baseline, 6-month and 12-months.	Self-report	G1: 68/92 (73.9) G2: 64/86 (74.4)	G1: 68/92 (73.9) G2: 64/86 (74.4) OR: 0.93 (0.46 to 1.90), adjusted OR: 1.60 (0.50 to 2.33) Adjusted p: 0.89
Rich et al., 1996[42] NA	≥80% compliance by method 2	30 days +/- 2 days after discharge; 1 time; NA	Pill count	G1: 80 G2: 76	Overall: 74.7% G1: 82.5% G2: 66.2% 95% CI, NR p: 0.033
Stacy et al., 2009[56] NA	Continuous persistence +Medication possession ratio =/>80%	6 months from baseline; 1 time; NA	PRD	G1: 253 G2: 244	G1: 45.1% G2: 37.3% Unadjusted OR (90% CI): 1.38 (1.03 to 1.86) Adjusted OR (90%CI): 1.41 (1.03 to 1.92) p: <0.10
Vivian et al., 2002[58] NA	Compliance survey at 6 months: When your medication does not seem to be working, how often do you take more than your health care provider prescribed? (>=once/wk)	Varied b/t groups; compliance measured in G1 at monthly visits, only measured at baseline and study end for G2	Self-report	G1: 26 G2: 27	G1: 8% G2: 8% 95% CI, NR p: 1.00

Author, Year Trial Name	Medication Adherence Outcome 4	Description of Timing of Measurement of Adherence Outcome 4	Data Source	N	Results
Wilson et al., 2010[65] Better Outcomes of Asthma Treatment (BOAT)	Controller regimen anti-inflammatory potency - mean equivalents of acquisition of beclome-thasone canister equivalents - year 1	Measured as aggregate for entire year	PRD	G1: 204 G2: 202 G3: 204	G1: 10.9 G3: 5.2; Group difference: 5.8 95% CI, 4.5 to 7.0 p< 0.0001 G1: 10.9 G2: 9.1; Group difference: 1.8 95% CI, 0.57 to 3.1 p: 0.005 G2: 9.1 G3: 5.2 Group difference: 3.9 95% CI, 2.6 to 5.2 p: <0.0001

Table D13. Medication adherence outcomes 5

Author, Year Trial Name	Medication Adherence Outcome 5	Description of Timing of Measurement of Adherence Outcome 5	Data Source	N	Results
Hoffman et al., 2003[18] NA	Percent adherence using HEDIS guidelines, at 6 months	Measured once at 6 months; adherence defined as a total of 51 gap days since beginning treatment (days 1-180)	PRD	G1: 4889 G2: 4665	G1: 31.5 G2: 29.4 95% CI, NR p: < 0.05
Katon et al., 1996[25] NA	A dosage of antidepressant medication for at least 90 days at or above lowest dosage recommended by AHCPR guidelines	NR	□PRD	G1: 76 G2: NS	Major Depression Group, for at least 30 days (% adherent) G1: 62.1% G2: 54.6% p=.55 Minor Depression Group, for at least 30 days (% adherent) G1: 69.6% G2: 39.5% p=0.08

Author, Year Trial Name	Medication Adherence Outcome 5	Description of Timing of Measurement of Adherence Outcome 5	Data Source	N	Results
Montori et al., 2011[35] NA	Started bisphosphonates	Measured at baseline	PRD	G1: 52 G2: 48	Total G1: 44% G2: 40% 95% CI, NR p: NR <10% Risk Category G1: 50% G2: 25% 95% CI, NR p: NR 10-30% Risk Category G1: 45% G2: 45% 95% CI, NR p: NR >30% Risk Category G1: 40% G2: 33% 95% CI, NR p: NR
Murray et al., 2007[36] NA	Refill adherence: Medication possession ratio (meds received relative to meds prescribed)	Results calculated for 1 yr, incorporating the 9 month intervention and 3 month post-intervention period; Presume that since refills were every 2 months, there were 6 measurements every 2 months	PRD	G1: NR G2: NR	G1: 109.4% G2: 105.2% 95% CI, NR Difference: 4.2% p: 0.007
Pyne et al., 2011[41] HIV Translating Initiatives for Depression Into Effective Solutions (HITIDES)	Antidepressant prescription rates (of providers) at 6 months	Not clear whether self-report or other method. 3 measurements taken: baseline, 6-month and 12-months.	Other	G1: 72/108 (66.7) G2: 78/115 (67.8)	G1: 72/108 (66.7) G2: 78/115 (67.8) OR: 0.89 (0.49 to 1.78); adjusted OR; 0.89 (0.46 to 1.74)
Rich et al., 1996[42] NA	Number of patients with >90% medication compliance (unclear which method used to calculate)	30 days +/- 2 days after discharge; 1 time; NA	Pill count	G1: 80 G2: 76	G1: 45 G2: 26 95% CI, NR p: 0.032

Author, Year Trial Name	Medication Adherence Outcome 5	Description of Timing of Measurement of Adherence Outcome 5	Data Source	N	Results
Rudd et al., 2004[45] NA	Proportion of medications taken correctly among those on a >=2 times-daily dosing regimen	1 day; daily ; 6 months	MEMS	NR	G1: 69% (34%) G2: 49% (41%) 95% CI, NR p: NR, not significant per text
Stacy et al., 2009[56] NA	6 month point prevalence persistency (For those prescribed a lipid-lowering agent in the 7-12 month period prior to the index statin): subject being in possession of a statin at the end of the 180-day observation period	6 months after baseline; 1 time; N/A	PRD	Overall N: 54 SG1: NR SG2: NR	SG1: 66.7% SG2: 37.0% 95% CI, NR p: <0.05
Vivian et al., 2002[58] NA	Compliance survey at 6 months: If answered yes to being away from home overnight in last 3 months, did you forget to take your medication when you were away from home overnight?, % who answered sometimes (2-3 times/wk) and always (>3 times/wk)	varied b/t groups; compliance measured in G1 at monthly visits, only measured at baseline and study end for G2	Self-report	G1: 26 G2: 27	G1: 15% G2: 10% 95% CI, NR p: 1.00
Wilson et al., 2010[65] Better Outcomes of Asthma Treatment (BOAT)	Controller regimen anti-in?ammatory potency - acquisition of beclomethasone canister equivalents - year 2	Measured as aggregate for entire year	PRD	G1: 204 G2: 202 G3: 204	G1: 7.1 G3: 4.6 Group difference: 2.5 95% CI, 1.2 to 3.8 p= 0.0002 G1: 7.1 G2: 5.8; Group difference: 1.4 95% CI, 0.04 to 2.7 p: 0.04 G2: 5.8 G3: 4.6 Group difference:1.1 95% CI, -0.18 to 2.4 p: >.05

Table D14. Medication adherence outcomes 6

Author, Year Trial name	Medication Adherence Outcome 6	Description of Timing of Measurement of Adherence Outcome 6	Data Source	N	Results
Hoffman et al., 2003[18] NA	Persistency (defined as the time span a patient continued taking the antidepressant prescription during the study. If the date of the last prescription filled plus the days' supply was ≤10 days from the end of the study, the patient was considered to be persistent)	Measured for previous 30 days, at 2, 3, 4, 5, and 6 months	PRD	G1: 4889 G2: 4665	**At 2 months**: G1: 45.9 G2: 44.3 **At 3 months:** G1: 36.8 G2: 35.3 **At 4 months:** G1: 30.2 G2: 28.9 **At 5 months**: G1: 28.8 G2: 27.3 **At 6 months:** G1: 24.9 G2: 23.4 95%Cis & p: NR **From 1-90 days**: Mean percent (SD): G1: 36.8 (24.3) G2: 35.3 (12.4) Chi-square: 0.127 95% CI, NR p: NR **From 1-180 days**: Mean percent (SD): G1: 24.9 (51.9) G2: 23.3 (51.9) Chi-square: 0.067 95% CI, NR p: NR
Murray et al., 2007[36] NA	Self-reported adherence from questionnaire at baseline and 9 month to compute a composite score of self-reported adherence	Measured at 1 month prior to intervention (baseline) and at month 9	Self-report	G1: NR G2: NR	G1: 1.0 G2: 0.8 95% CI, NR p: 0.48

Author, Year Trial name	Medication Adherence Outcome 6	Description of Timing of Measurement of Adherence Outcome 6	Data Source	N	Results
Pyne et al., 2011[41] HIV Translating Initiatives for Depression Into Effective Solutions (HITIDES)	antidepressant prescription rates (of providers) at 12 months	Not clear whether self-report or other method. 3 measurements taken: baseline, 6-month and 12-months.	Other	G1: 65/105 (61.9) G2: 69/110 (62.7)	G1: 65/105 (61.9) G2: 69/110 (62.7), OR: 0.93 (0.49-1.78); adjusted OR: 0.93 (0.49-1.78) Adjusted p: 0.93
Stacy et al., 2009[56] NA	6 month point prevalence persistency: subject being in possession of a statin at the end of the 180-day observation period (For those with continuous persistance + MPR=>80%)	6 months after baseline; 1 time; N/A	PRD	Overall N:NR SG1: NR SG2: NR	SG1: 25.9% SG2: 3.3% 95% CI, NR p: <0.05
Vivian et al., 2002[58] NA	% that received refills for antihypertensive agents within 2 weeks of the next scheduled refill date	NR	PRD	G1: 26 G2: 27	G1: 85% G2: 93% 95% CI, NR p: >0.42
Wilson et al., 2010[65] Better Outcomes of Asthma Treatment (BOAT)	Medication acquisition at Year 1 and Year 2 -for long-acting beta agonists (LABA) Fill/refill adherence was measured using a continuous medication acquisition (CMA) index for each year, calculated as the total days' supply acquired in a given year divided by 365 days	Measured as aggregate for year; at Year-1 follow-up and Year 2 follow-up	PRD	N for Year 1: G1: 40 G2: 44 G3: 52 N for Year 2: G1:112 G2: 108 G3:59	Group differences YEAR 1: G1-G3: 0.11 95% CI, 0.02 to 0.20 G1-G2: 0.09 95% CI, 0.02 to 0.17 G2-G3: 0.01 95% CI, -0.08 to 0.11 YEAR 2: G1-G3: 0.11 95% CI, 0.01 to 0.20 G1:G2: 0.09 95% CI, 0.01 to 0.18 G2-G3: 0.01 95% CI, -0.08 to 0.11

Table D15. Medication adherence subgroup outcomes, part 1

Author, Year Trial Name	Subgroup	Specific subgroup	Medication Adherence Outcome 1 for subgroup	Description of Timing of Measurement of Adherence Outcome	Data source	N	Results
Bogner et al., 2008[4] NA	Hypertension comorbidity	Hypertension comorbidity	Depression adherence: % of prescribed doses taken; calculated as number of doses taken divided by the number of doses prescribed during the observation period multiplied by 100% - dichotomized with 80% threshold	Measured over 6 week study period for entire study period	MEMS	G1: 32 G2: 32	G1: 23 (71.9) G2: 10 (31.3) 95% CI, p: .001
Bogner et al., 2010[5] NA	Older African American primary care patients	Older African American primary care patients	>80% adherence to an oral hypoglycemic agent	4 times, biweekly beginning at baseline and ending at week 6	MEMS	G1: 29 G2: 29	**BL** G1: 10 (34.5%) G2: 6 (20.7%) 95% CI, NR p: 0.19 **EP at 6 weeks** G1: 18 (62.1%) G2: 7 (24.1%) 95% CI, NR p: 0.004

Author, Year Trial Name	Subgroup	Specific subgroup	Medication Adherence Outcome 1 for subgroup	Description of Timing of Measurement of Adherence Outcome	Data source	N	Results
Fulmer et al., 1999[15] NA	Elderly	Elderly	Percent of prescribed medication doses taken	Adherence was monitored during a 2-week pre-intervention phase, 6-week intervention phase (time 2), and 2-week post-intervention phase (time 3)	MEMS	G1: 17 G2: 15 G3: 18	**Average compliance rates at BL** G1: 82% G2: 76% G3: 81% **Average compliance rates at time 3** G1: 84% G2: 74% G3: 57% (significantly decreased from baseline at p<0.04) 95% CI, p: There was a statistically significant time effect during the course of the study from baseline to post-intervention (F=4.08, p<0.05). Over time, G1 and G2 showed enhanced compliance relative to G3. However, there was no significant difference between G1 and G2.

Author, Year Trial Name	Subgroup	Specific subgroup	Medication Adherence Outcome 1 for subgroup	Description of Timing of Measurement of Adherence Outcome	Data source	N	Results
Katon et al., 1995[24] NA	Major depression	Major depression	% receiving adequate dosage of antidepressants for ≥30 days (details NR)	during continuation phase of treatment (3-7 months)	PRD	**Major depression group** N=91 **Minor depression group** N=126	**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
Katon et al., 1996[25] NA	Major depression	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction
Katon et al., 1999[26] NA Katon et al., 2002[27] NA	Severity of Depression (reported in 3169 Katon)	Severe depression (Defined as SCL-20 score >2.0 at baseline)	Adherence to adequate dosage of antidepressants for at least 90 days out of previous six months	Timeframe: six months; measured 5 times in 6 month-intervals until 30 months after randomization (at 6, 12, 18, 24, 30 months)	PRD	Overall N: 79 G1: NR G2: NR	**At 6 months**: G1: 24 (72%) G2: 14 (40%) Chi-square (1) = 8.23 p: < 0.01 **At 12 months**: G1: 23 (70%) G2: 13 (37%) Chi-square (1) = 5.98 p: < 0.05 For 18-, 24- and 30-months: "the percentages were very similar for the treatment groups"

Author, Year Trial Name	Subgroup	Specific subgroup	Medication Adherence Outcome 1 for subgroup	Description of Timing of Measurement of Adherence Outcome	Data source	N	Results
Lee et al., 2006[31] FAME	Elderly (≥65 years old)	Elderly (≥65 years old)	% medication adherence at 14 months (proportion of pills taken), mean (SD)	Total timeframe of 6 month average (months 8-14); G1 - 3 pill counts every 2 months; G2 - 1 pill count at the end of 6 months	Pill count	G1: 83 G2: 76	G1: 95.5 (7.7) G2: 69.1 (16.4) 95% CI, NR p<0.001

Author, Year Trial Name	Subgroup	Specific subgroup	Medication Adherence Outcome 1 for subgroup	Description of Timing of Measurement of Adherence Outcome	Data source	N	Results
Lin et al., 2006[32] NA	Depression comorbidity	Depression comorbidity	Percentage of days nonadherent	Measured 2 times over a 12-month period	PRD	Oral hypoglycemic agent **BL** G1: 103 G2: 103 **EP** G1: 103 G2: 103 ACE inhibitor **BL** G1: 54 G2: 65 **EP** G1: 59 G2: 52 Lipid-lowering agent **BL** G1: 50 G2: 52 **EP** G1: 54 G2: 63	Oral hypoglycemic agent **BL** (%) (Mean (SD)) G1: 19.8% (21.3%) G2: 22.9% (24.0%) 95% CI, NR p: NS **EP** (%) (Mean (SD)) G1: 28.2% (28.9%) G2: 24.0% (24.7%) 95% CI, NR p: <0.03 ACE inhibitor **BL** (%) (Mean (SD)) G1: 27.4% (27.1%) G2: 29.7% (29.3%) 95% CI, NR p: NS **EP** (%) (Mean (SD)) G1: 24.2% (22.7%) G2: 18.9% (17.4%) 95% CI, NR p: NS Lipid-lowering agent **BL** (%) (Mean (SD)) G1: 29.3% (26.7%) G2: 24.5% (23.0%) 95% CI, NR p: NS **EP** (%) (Mean (SD)) G1: 28.8% (27.1%) G2: 27.7% (24.0%) 95% CI, NR p: NS

Author, Year Trial Name	Subgroup	Specific subgroup	Medication Adherence Outcome 1 for subgroup	Description of Timing of Measurement of Adherence Outcome	Data source	N	Results
Pyne et al., 2011[41] HIV Translating Initiatives for Depression Into Effective Solutions (HITIDES)	Entire study is conducted in subgroup with HIV comorbidity	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction
Rich et al., 1996[42] NA	Elderly (≥70 years old)	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction
Schneider et al., 2008[49] NA	Elderly (≥65 years old)	Elderly (≥65 years old)	Percentage of patients who had prescriptions refilled on time (±5 days of due date)	Calculated for all previous months at 6 month and 12 month follow-ups	PRD	SG1: 47 SG2: 38	Mean (SD) SG1: 80.4 (21.2) SG2: 66.1 (28.0) 95% CI, N-R p: 0.12
Zhang et al., 2010[67] N/A	Elderly (≥65 years)	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction

Table D16. Medication adherence subgroup outcomes, part 2

Author, Year Trial name	Subgroup	Specific Subgroup	Medication Adherence Outcome 1 for subgroup	Description of Timing of Measurement of Adherence Outcome	Data Source	N	Results
Bogner et al., 2008[4] NA	Hypertension comorbidity	Hypertension comorbidity	Hypertension adherence: % of prescribed doses taken; calculated as number of doses taken divided by the number of doses prescribed during the observation period multiplied by 100% - dichotomized with 80% threshold	Measured over 6 week study period for entire study period	MEMS	G1: 32 G2: 32	G1: 25 (78.1) G2: 10 (31.3) 95% CI, p: <.001
Bogner et al., 2010[5] NA	Older African American primary care patients	Older African American primary care patients	>80% adherence to an antidepressant	4 times, biweekly beginning at baseline and ending at week 6	MEMS	G1: 29 G2: 29	**BL** G1: 8 (27.6%) G2: 4 (13.8%) 95% CI, NR p: 0.17 **EP at 6 weeks** G1: 18 (62.1%) G2: 3 (10.3%) 95% CI, NR p: <0.001
Katon et al., 1996[25] NA	Major depression	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction

Author, Year Trial name	Subgroup	Specific Subgroup	Medication Adherence Outcome 1 for subgroup	Description of Timing of Measurement of Adherence Outcome	Data Source	N	Results
Katon et al., 1999[26] NA Katon et al., 2002[27] NA	Severity of Depression (reported in 3169 Katon)	Moderate depression (defined as SCL-20 score between 1.0-2.0)	Adherence to adequate dosage of antidepressants for at least 90 days out of previous six months, measured twice at 6 & 12 months	Timeframe: six months; measured twice, at 6 months and 12 months after study began	PRD	Overall N: 149 G1: NR G2: NR	**6 months**: G1: 76% G2: 46% Chi-square (1)= 6.10 p: < 0.05 **12 months**: NR "Similar, but nonsignificant, trends were observed for the second 6-month block." For 18-, 24- and 30-months: "the percentages were very similar for the treatment groups"
Lee et al., 2006[31] FAME	Elderly (≥65 years old)	Elderly (≥65 years old)	≥80% adherence to all medications, %	last 2 months; 4 times (including baseline at 8 months); 2 months	Pill count	G1: 77 G2: 69	G1: 97.4 G2: 21.7 95% CI, NR p<0.001

Author, Year Trial name	Subgroup	Specific Subgroup	Medication Adherence Outcome 1 for subgroup	Description of Timing of Measurement of Adherence Outcome	Data Source	N	Results
Lin et al., 2006[32] NA	Depression comorbidity	Depression comorbidity	Adjusted mean difference in percentage of days nonadherent (baseline minus endpoint)	NA	PRD	Oral hypoglycemic agent **BL** G1: 103 G2: 103 Endpoint G1: 103 G2: 103 ACE inhibitor **BL** G1: 54 G2: 65 **EP** G1: 59 G2: 52 Lipid-lowering agent **BL** G1: 50 G2: 52 **EP** G1: 54 G2: 63	**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
Pyne et al., 2011[41] HIV Translating Initiatives for Depression Into Effective Solutions (HITIDES)	Entire study is conducted in subgroup with HIV comorbidity	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction
Rich et al., 1996[42] NA	Elderly (≥70 years old)	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction

Author, Year Trial name	Subgroup	Specific Subgroup	Medication Adherence Outcome 1 for subgroup	Description of Timing of Measurement of Adherence Outcome	Data Source	N	Results
Schneider et al., 2008[49] NA	Elderly (≥65 years old)	Elderly (≥65 years old)	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 1st and last rx dispensing)	Calculated for all previous months at 6 month and 12 month follow-ups	PRD	G1: 47 G2: 38	Mean (SD) G1: 0.93 (11.4) G2: 0.87 (14.2) 95% CI, p: 0.039
Zhang et al., 2010[67] N/A	Elderly (≥65 years)	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction

Table D17. Intervention components, part 1

Author, Year Trial Name	Target of the Intervention	Intensity	Agent Delivering the Intervention	Duration	Delivery Mode	Knowledge-Based	Awareness-Based
Bender et al., 2010[1] NA	Patient	2-3 calls, each call less than 5 minutes	Automated phone service	2-3 calls over 10 weeks	Automated phone service	Yes	Yes
Berg et al., 1997[2] NA	Patient	2 hours	Nurse experienced with asthma	6 training sessions over 7 weeks	Face-to-face	Yes	No
Berger et al., 2005[3] NA	System and patient	NR	Biogen call center staff	Every 2 weeks or every 4 weeks (depending on stage of readiness) for 3 months	Phone, and counselors were guided through the sessions by web-based software	No	No
Bogner et al., 2008[4] NA	Patient, system	3, 30-minute in-person sessions and 2, 15-minute telephone-monitoring contacts during a 4-week period	Integrated care manager	3, 30-minute in-person sessions and 2, 15-minute telephone-monitoring contacts during a 4-week period	Face to face and telephone	Yes	No
Bogner et al., 2010[5] NA	Patient	2 hours of total contact time during the study = three 30-minute sessions and two 15-minute contacts	Other = Integrated care manager	5 sessions over a 4-week period	Face-to-face, over-the-phone	Yes	Yes
Bosworth et al., 2005[6] V-STITCH	Patient	2 years, 6 month outcomes reported in this paper	Nurse	Bimonthly for 2 years	Telephone	Yes	Yes
Bosworth et al., 2008[7] TCYB Bosworth et al., 2007[8] TCYB Methods paper	Patient	2 years, this paper reports 6 month outcomes	Nurse	bimonthly for 2 years	telephone	Yes	Yes

Author, Year Trial Name	Target of the Intervention	Intensity	Agent Delivering the Intervention	Duration	Delivery Mode	Knowledge-Based	Awareness-Based
Capoccia et al., 2004[9] NA	Patient	Median 15 min per intervention, range 5-50 min	clinical pharmacist or pharmacy resident	Follow up was weekly phone calls for the first 4 weeks followed by phone contact every 2 weeks through week 12. During months 4–12,subjects received a phone call every other month	Phone	Yes	Yes
Carter et al., 2009[10] NA	Patients, pharmacists, physicians	Teambuilding exercises involving physicians and pharmacist. Pharmacists were encouraged to assess meds and BP at baseline, one month plus over the telephone at 3 months and more frequently if needed.	Clinical pharmacists	Varied. Average of 1.6 (1.4) additional visits/contacts per patient over the 6-month study period	Face-to-face, telephone	Yes	No
Chernew et al., 2008[11] NA	Patient	NA	NA	NA	NA	No	No
Choudhry et al., 2010[12] NA	Combination: patients & policy	Indefinite (policy change)	Large Fortune 500 company	NA	NA	No	No
Choudhry et al., 2011[13] MI FREEE	Policy	NA	NA	NA	Cost of prescription medications	No	No
Friedman et al., 1996[14] NA	Patient	Weekly calls, average length 4 minutes	Other: automated telephone/computer system	Mean number of actual calls is not reported. Patients were instructed to call in weekly for a 6-month period (24 calls in 6 months)	Telephone	Yes	Yes
Fulmer et al., 1999[15] NA	Patient	3-5 minute phone calls	Research assistant	daily calls for 6 weeks	G1: Video/phone G2: Phone	No	No
Grant et al., 2003[16] NA	Combination [patient, provider]	Mean of 18.5 +/- 8.8 (sd) minutes	Pharmacist	1	Over-the-phone	Yes	No

Author, Year Trial Name	Target of the Intervention	Intensity	Agent Delivering the Intervention	Duration	Delivery Mode	Knowledge-Based	Awareness-Based
Guthrie et al., 2001[17] First Myocardial Infarction (MI) Risk Reduction Program	Patient	6 months	NA	5 over 6 months	Telephone, mail	Yes	Yes
Hoffman et al., 2003[18] NA	Patient & Provider	Monthly mailings to each	NA	6 mailings, once a month, over 6 months	Education letter for patients and providers	Yes	No
Hunt et al., 2008[19] NA	Patient	One appointment, length not specified, additional appointments if needed	Pharmacist	The intervention group received a mean of 4 (2.3) pharmacy visits per patient, but it is not clear if these are all study related visits.	Face to face	Yes	Yes
Janson et al., 2003[20] NA	Patient	30 minutes each	Advanced practice nurse	5 visits over 7 weeks	Face-to-face	Yes	Yes
Janson et al., 2009[21] NA	Patient	4-week run-in with biweekly visits; 3 identical 30-minute visits after randomization	Trained advanced practice nurse and respiratory therapist, both certified asthma educator	4-week run-in with biweekly visits; 3 identical 30-minute visits after randomization; 4-week intervention period of biweekly visits was followed by 14 weeks of observation, with visits held at 4-week intervals (3 visits)	Face-to-face	Yes	Yes
Johnson et al., 2006[23] NR	Patient	6 months	computer-generated intervention mailed to participants	3 times over 6 months (0, 3 and 6 months)	Computer; mail	Yes	Yes
Johnson et al., 2006[22] NR	Patient	6 months	computer-generated	3 times over 6 months	Computer; mail	Yes	Yes

Author, Year Trial Name	Target of the Intervention	Intensity	Agent Delivering the Intervention	Duration	Delivery Mode	Knowledge-Based	Awareness-Based
Katon et al., 2001[28] NA Ludman et al., 2003[29] NA Van Korff et al., 2003[30] NA	Patient, Provider, system	2 in-person visits (90 min. and 60 min); 3 telephone calls; 4 mailings. Intensity of calls not specified	psychologist, Psychiatric nurse, & social worker trained as "depression prevention specialists"	2 in-person visits; 3 telephone calls at 2, 5, 9 months; 4 personalized mailings at 3, 6, 10, and 12 months	Face-to-face, written material, DVD, over-the-phone	Yes	Yes
Katon et al., 1995[24] NA	Patient, provider, system	Brief print materials and 20-minute video prior to PCP visit, 15 extra minutes during PCP visit, 2 visits with psychiatrist (50 and 20 minutes)	PCP, psychiatrist	2 PCP visits and 2 psychiatrist visits over 4-6 weeks with appointments spaced 7-10 days apart	Face-to-face, written material, video	Yes	No
Katon et al., 1996[25] NA	Combination: patient, provider, system	A 1 hour initial planning visit and 3 to 5 half hour contacts (total time ranged from 2.5 to 3.5 hours). Patients attended a mean (SD) of 5.2 (1.7) visits and received a mean of (SD) of 3.4 (1.3) telephone calls	Psychologist	direct contact phase began 1 week after initiation and ended 3 to 6 weeks after; telephone contacts occurred at 2, 4, 12, and 24 weeks after the end of direct contact phase	Face to face, telephone, written material, videos	Yes	Uncertain
Katon et al., 1999[26] NA Katon et al., 2002[27] NA	Combination: patient, provider, system	At least 2 visits with psychiatrist: 50-minutes (initial) and 25 minutes (follow-up)	Psychiatrist	At least 2 in-person visits; (mean 2.75; range 0-7) and follow-up telephone calls (mean 1.56; SD 1.61) calls	Face-to-face, written material, DVD, over-the-phone	Yes	Uncertain
Lee et al., 2006[31] FAME	Patient	12 months (includes phase 1)	Pharmacists	Every 2 months for 12 months (includes phase 1)	Face-to-face	Yes	No
Lin et al., 2006[32] NA	Patients	4 hours for weeks 0-12; Contact time between weeks 12-52 = monthly	Nurses	Weeks 0-12 = 7 sessions total (1 initial hour-long visit + 2 sessions per month for the first 3 months); Weeks 13-52 = 9 monthly visits	Face-to-face, telephone	No	No

Author, Year Trial Name	Target of the Intervention	Intensity	Agent Delivering the Intervention	Duration	Delivery Mode	Knowledge-Based	Awareness-Based
Maciejewski et al., 2010[33] NA	Policy	NA	Insurer (Blue Cross Blue Shield of North Carolina)	NA	NA	No	No
Mann et al., 2010[34] The Statin Choice	Patient	6 minutes one time	Physician	1	Face to face with written materials	Yes	Yes
Montori et al., 2011[35] NA							
Murray et al., 2007[36] NA	Patient	9 months	Pharmacist	Sessions not quantified, 9 month duration intervention	Face-to-face, written material	Yes	No
Nietert et al., 2009[37] NA	Patients	NR	Pharmacists	NR	Telephone, fax	Yes	Uncertain
Okeke et al., 2009[38] NA	Patient	Video: 1 video, 10 minutes in length; 1 discussion, length NR; phone calls at weeks 1-5, 7, and 9, length NR; alarms on dosing aid for 3 months	video, dosing aid, study coordinator (level of training NR)	3 months	Video, face-to-face discussion, phone calls, dosing aid device	Yes	No
Pearce et al., 2008[39] Cardiovascular Risk Education and Social Support (CaRESS) Trial	Patient	30 minutes with patient and their support person once during the study	Registered nurse patient educator; Other = Support person chosen by the patient according to study criteria	1 session over a 12-month period	Face-to-face	No	No
Powell et al., 1995[40] NA	Patients	One 30-minute videotape per drug per subject	NA	NR	Mail	Yes	No
Powers et al., 2011[68] NA	Patient	3 months	NR	NR	Face-to-face; written material	Yes	Yes

Author, Year Trial Name	Target of the Intervention	Intensity	Agent Delivering the Intervention	Duration	Delivery Mode	Knowledge-Based	Awareness-Based
Pyne et al., 2011[41] HIV Translating Initiatives for Depression Into Effective Solutions (HITIDES)	Patient and provider	intensity of interaction with providers not documented; for patients, depression case managers conducted telephone-based monitoring every 2 weeks during acute treatment (before achieving a sustained 50% decrease in PHQ-9 score) and every 4weeks during watchful waiting or continuation treatment (for 2months after maintaining remission [PHQ-9 score, 5] or 6 months after maintaining a 50% decrease in the PHQ-9 score)	Team of nurse depression care manager, clinical pharmacist, and psychiatrist	NR	For patients: telephone; For providers: electronic medical records	Yes	Yes
Rich et al., 1996[42] NA	Patient	1 month	Multidisciplinary: RN, social worker, dietician, MD, and pharmacists	As long as pts were in the hospital - varied and visits not quantified	Face-to-face, written material	Yes	Yes
Rickles et al., 2005[43] NA	Patient	3 phone calls, each lasted on average 11-19 minutes	Pharmacist	3 mo.	Phone	Yes	Yes
Ross et al., 2004[44] NR	Combination [patient, system]	12 months	NA	NA	Computer	Yes	No
Rudd et al., 2004[45] NA	Combination [patient, system of care]	6 months	Nurse	5 times over 6 months (baseline, 1 wk, 1 mo, 2 mos, 4 mos)	Telephone	Yes	Yes
Rudd et al., 2009[46] NA	Patient	The two health educator sessions could last up to an hour each (average 20 minutes)	Health educator, print materials	Two sessions over an unspecified time period (coincided with rheumatology appointments) and optional additional phone and in-person contact for 6 months	Face-to-face, written material, optional over-the-phone	Yes	No

Author, Year Trial Name	Target of the Intervention	Intensity	Agent Delivering the Intervention	Duration	Delivery Mode	Knowledge-Based	Awareness-Based
Schaffer et al., 2004[47] NA	Patient	30-60 min	Audio or book	1	Audio or book	Yes	Yes
Schectman et al., 1994[48] NA	Patient	28 days	Certified medical assistant	5 calls over 28 days	Telephone	No	Yes
Schneider et al., 2008[49] NA	Patient	NA	NA	NA	Packaging	No	No
Schnipper et al., 2006[50] NA	Combination: system and patient	NR	Pharmacist	1 in-person session, 1 follow-up phone call	Face-to-face, phone	Yes	No
Simon et al., 2006[51] NA	Patient and provider	contacted initially within two weeks of randomization; 2 additional telephone contacts occurred four and 12 weeks later; phone calls lasted approx. 20 min.	Registered nurses with a minimum of five years' experience in inpatient or outpatient mental health practice	3 sessions - baseline, end of month 1, end of month 3	Phone; treating psychiatrist received a structured report of each contact with recommendations	Yes	Yes
Sledge et al., 2006[52#2608] NA	Combination: provider and patient	2-3 hour session, 1 year of ambulatory care including minimum of monthly phone calls and phone/pager availability 5d/wk	Social worker, psychiatrist, general internist, case manager	at least 1 in-person session and 12 phone calls	Face-to-face, phone, home visits prn, written report and discussion between case manager and PCP	Uncertain	Uncertain
Smith et al., 2008[53] NR	Provider, patient	2 months	Health plan physician administrator	2 mailings over 2 months	Written material, mail	Yes	Yes
Solomon et al., 1998[54] NA Gourley et al., 1998[55] NA	Patient	6 months	Pharmacist	5 sessions over 6 months, plus education and help as needed	Face-to-face, additional telephone support	Yes	No
Stacy et al., 2009[56] NA	Patient	6 months	NA	3 calls over 6 months	Phone, mail, written material	Yes	Yes

Author, Year Trial Name	Target of the Intervention	Intensity	Agent Delivering the Intervention	Duration	Delivery Mode	Knowledge-Based	Awareness-Based
Taylor et al., 2003[57] NA	Patient, provider	20 minutes	Pharmacist	before each regular clinic visit during 12-month period	Face-to-face, written material, recommendations to provider	yes	No
Vivian et al., 2002[58] NA	Patient, system	6 months	Pharmacist	monthly over 6 months	Face-to-face	Yes	Yes
Waalen et al., 2009[59] NA	Patient	Care from physician assistant: NR; phone open-ended discussion: NR; follow-up phone calls: 5 minutes monthly until regimen started and no problems reported	Physician Assistant under supervision of a preventive medicine physician (EMB)	After initial visit, monthly phone calls until prescription was filled and no problems reported	Face-to-face care, written material, phone conversations	Yes	No
Wakefield et al., 2011[60] NA	Patient	12 months	nurse	NA	Telehealth device	Yes	Yes
Weinberger et al., 2002[61] NA	Provider (pharmacist)	NR	NR; the initial pharmacist training conducted by 'investigators representing several backgrounds'	NA	Primarily computer-based, but also included face-to face training and written materials	Yes	No
Weymiller et al., 2007[62] Statin Choice Randomized Trial Jones et al., 2009[63] Statin Choice Randomized Trial	Patients	Brief but unspecified contact time either before scheduled visits with clinicians or during their visits	Researcher-diabetologists or physician faculty/fellows specializing in endocrinology	One session over the 3-month study period	Face-to-face	Yes	Uncertain
Williams et al., 2010[64] NA	Providers	adherence data provided to providers every 2 weeks	electronic data	NR	Electronic data	Yes	No

Author, Year Trial Name	Target of the Intervention	Intensity	Agent Delivering the Intervention	Duration	Delivery Mode	Knowledge-Based	Awareness-Based
Wilson et al., 2010[65] Better Outcomes of Asthma Treatment (BOAT); note that there is online supplemental material for methods and timeline	Patient; Patient-provider communication	Initial study visit: 1.5 hour; 2nd visit: 30 minutes. Follow-up phone calls: 30 minutes total.	Nurses, respiratory therapists, and pharmacists, as well as nurse practitioners and physician assistants, most of whom already served as asthma care managers, were recruited to serve as study care managers	2 sessions and 3 brief phone calls at 3, 6, 9 months	Face-to-face and phone	Yes	Yes
Wolever et al., 2010[66] NA	Patient	30 minutes per intervention session	Other - coaches	14 sessions over 6 months	Over-the-phone	Uncertain	Uncertain
Zhang et al., 2010[67] NA	Patient	NA	NA	NA	NA	No	No

Table D18. Intervention components, part 2

Author, Year Trial Name	Social Influence	Targets Attitudes	Self-efficacy	Specify Other Self-Efficacy Components	Intention Formation	Action control	Maintenance
Bender et al., 2010[1] NA	No	No	No	NA	No	No	No
Berg et al., 1997[2] NA	No	No	Yes	NA	No	No	No
Berger et al., 2005[3] NA	No	No	No	NA	No	No	No
Bogner et al., 2008[4] NA	No	Yes	No	Na	No	No	No
Bogner et al., 2010[5] NA	No	No	Yes	NA	Yes	Uncertain	Uncertain
Bosworth et al., 2005[6] V-STITCH	No	No	No	NA	Yes	Yes	Yes
Bosworth et al., 2008[7] TCYB Bosworth et al., 2007[8] TCYB Methods paper	No	Yes	No	NA	Yes	Yes	No
Capoccia et al., 2004[9] NA	No	No	No	NA	Yes	Uncertain	Uncertain
Carter et al., 2009[10] NA	No	No	No	NA	No	No	No
Chernew et al., 2008[11] NA	No	No	No	NA	No	No	No
Choudhry et al., 2011[13] MI FREEE	No	No	No	No	No	No	No
Choudhry et al., 2010[12] NA	No	No	No	NA	No	No	No
Friedman et al., 1996[14] NA	No	No	No	NA	Uncertain	Uncertain	Uncertain
Fulmer et al., 1999[15] NA	No	No	No	No	No	Yes	No
Grant et al., 2003[16] NA	No	No	No	NA	No	No	Yes
Guthrie et al., 2001[17] First Myocardial Infarction (MI) Risk Reduction Program	No	No	No	NA	No	Yes	No

Author, Year Trial Name	Social Influence	Targets Attitudes	Self-efficacy	Specify Other Self-Efficacy Components	Intention Formation	Action control	Maintenance
Hoffman et al., 2003[18] NA	No	No	No	No	No	Yes	No
Hunt et al., 2008[19] NA	Uncertain	Uncertain	No	NA	Uncertain	No	No
Janson et al., 2003[20] NA	No	No	Yes	NA	No	Uncertain	Yes
Janson et al., 2009[21] NA	No	No	Yes	NA	No	No	Uncertain
Johnson et al., 2006[23] NR	No	Yes	Yes	Provided information about the participant's level of temptation for not adhering	No	No	Yes
Johnson et al., 2006[22] NR	Yes	Yes	Yes	NA	No	No	No
Katon et al., 2001[28] NA Ludman et al., 2003[29] NA Van Korff et al., 2003[30] NA	No	Uncertain	Yes	Patients taught self-monitoring strategies; taught to identify and proactively plan for situations that would likely lead to relapse	Yes	Yes	Yes
Katon et al., 1995[24] NA	No	No	Yes	NA	No	No	No
Katon et al., 1996[25] NA	Uncertain	Uncertain	Yes	NA	Uncertain	Uncertain	Uncertain
Katon et al., 1999[26] NA Katon et al., 2002[27] NA	No	No	Yes	NA	No	No	No
Lee et al., 2006[31] FAME	No	No	No	NA	No	No	No
Lin et al., 2006[32] NA	No	Uncertain	No	NA	Yes	No	Yes
Maciejewski et al., 2010[33] NA	No	No	No	NA	No	No	No

Author, Year Trial Name	Social Influence	Targets Attitudes	Self-efficacy	Specify Other Self-Efficacy Components	Intention Formation	Action control	Maintenance
Mann et al., 2010[34] The Statin Choice	No	No	No	NA	No	No	No
Montori et al., 2011[35] NA	No	No	No	No	No	No	No
Murray et al., 2007[36] NA	No	No	Yes	Prescription-taking skills were assessed and addressed as needed; Coping responses including education and facilitation with RNs and MDs was provided	No	No	No
Nietert et al., 2009[37] NA	No	No	Uncertain	NA	No	No	No
Okeke et al., 2009[38] NA	No	No	No	NA	No	No	No
Pearce et al., 2008[39] Cardiovascular Risk Education and Social Support (CaRESS) Trial	Yes	Uncertain	Yes	NA	No	Yes	No
Powell et al., 1995[40] NA	No	No	No	NA	No	No	No
Powers et al., 2011[68] NA	No	Yes	No	NA	No	No	No
Pyne et al., 2011[41] HIV Translating Initiatives for Depression Into Effective Solutions (HITIDES)	Uncertain	No	Yes	instruction in self-management (e.g., encouraging patients to exercise and participate in social activities)	No	Yes	No
Rich et al., 1996[42] NA	No	No	No	NA	Yes	Yes	No
Rickles et al., 2005[43] NA	No	Uncertain	Uncertain	NA	Yes	Uncertain	Uncertain
Ross et al., 2004[44] NR	No	No	No	NA	No	No	No

Author, Year Trial Name	Social Influence	Targets Attitudes	Self-efficacy	Specify Other Self-Efficacy Components	Intention Formation	Action control	Maintenance
Rudd et al., 2004[45] NA	No	No	Yes	NA	Yes	No	Yes
Rudd et al., 2009[46] NA	No	No	No	NA	No	No	No
Schaffer et al., 2004[47] NA	No	Uncertain	Yes	NA	Uncertain	Uncertain	Uncertain
Schectman et al., 1994[48] NA	No	No	Yes	NA	No	No	No
Schneider et al., 2008[49] NA	No	No	No	No	No	Yes	No
Schnipper et al., 2006[50] NA	No	No	No	NA	No	No	No
Simon et al., 2006[51] NA	No	No	No	NA	Uncertain	Uncertain	Uncertain
Sledge et al., 2006[52#2608] NA	No	No	No	NA	No	Uncertain	No
Smith et al., 2008[53] NR	No	No	No	NA	No	No	No
Solomon et al., 1998[54] NA Gourley et al., 1998[55] NA	No	No	No	NA	No	No	No
Stacy et al., 2009[56] NA	No	Yes	Yes	NA	Yes	No	Yes
Taylor et al., 2003[57] NA	No	No	No	NA	No	No	No
Vivian et al., 2002[58] NA	No	No	No	NA	Yes	No	Yes
Waalen et al., 2009[59] NA	No	No	No	NA	No	No	No
Wakefield et al., 2011[60] NA	No	No	No	NA	No	No	No
Weinberger et al., 2002[61] NA	No	No	No	NA	No	Yes	No

Author, Year Trial Name	Social Influence	Targets Attitudes	Self-efficacy	Specify Other Self-Efficacy Components	Intention Formation	Action control	Maintenance
Weymiller et al., 2007[62] Statin Choice Randomized Trial Jones et al., 2009[63] Statin Choice Randomized Trial	No	No	No	NA	No	No	No
Williams et al., 2010[64] NA	No	No	No	NA	No	No	No
Wilson et al., 2010[65] Better Outcomes of Asthma Treatment (BOAT); Note that there is online supplemental material for methods and timeline	No	No	Yes	NA	Yes	No	No
Wolever et al., 2010[66] NA	No	Yes	Yes	NA	Yes	No	No
Zhang et al., 2010[67] NA	No	No	No	NA	No	No	No

Table D19. Intervention components, part 3

Author, Year Trial Name	Facilitation	Contingent Rewards	Motivational Interviewing	Stress Management	Organizational Learning Strategies	Systems Change: Clinical Champions	Systems Change: Total Quality Management/ Continuous Quality Improvement	Other	Number of Components
Bender et al., 2010[1] NA	No	No	No	No	No	No	No	NA	2
Berg et al., 1997[2] NA	No	No	No	No	No	No	No	NA	2
Berger et al., 2005[3] NA	No	No	yes	No	No	No	No	No	2
Bogner et al., 2008[4] NA	Yes	No	No	No	No	No	No	NA	3
Bogner et al., 2010[5] NA	Yes	No	No	No	No	No	No	NA	5
Bosworth et al., 2005[6] V-STITCH	Yes	No	No	No	No	No	No	positive-gain framing	7
Bosworth et al., 2008[7] TCYB Bosworth et al., 2007[8] TCYB Methods paper	Yes	No	Yes	No	No	No	No	NA	7
Capoccia et al., 2004[9] NA	yes	No	No	No	No	No	No	NA	3
Carter et al., 2009[10] NA	Yes	No	No	No	No	No	No	Role of pharmacist-physician collaboration	2
Chernew et al., 2008[11] NA	No	No	No	No	No	No	No	Copay reduction	1

Author, Year Trial Name	Facilitation	Contingent Rewards	Motivational Interviewing	Stress Management	Organizational Learning Strategies	Systems Change: Clinical Champions	Systems Change: Total Quality Management/ Continuous Quality Improvement	Other	Number of Components
Choudhry et al., 2010[12] NA	No	No	No	No	No	No	No	Policy change: reductions in medication cost sharing with company employees & beneficiaries	1
Choudhry et al., 2011[13] MI FREEE	No	No	No	No	No	No	No	Policy change--reducing costs of prescription medications	1
Friedman et al., 1996[14] NA	No	No	Yes	Uncertain	No	No	No	NA	3
Fulmer et al., 1999[15] NA	No	No	No	No	No	No	No	No	1
Grant et al., 2003[16] NA	No	No	No	No	No	No	No	email feedback to providers; offer of appointment making; social service referral as needed	4
Guthrie et al., 2001[17] First Myocardial Infarction (MI) Risk Reduction Program	No	No	No	No	No	No	No	NA	3

Author, Year Trial Name	Facilitation	Contingent Rewards	Motivational Interviewing	Stress Management	Organizational Learning Strategies	Systems Change: Clinical Champions	Systems Change: Total Quality Management/ Continuous Quality Improvement	Other	Number of Components
Hoffman et al., 2003[18] NA	No	No	No	No	No	No	No	Provider also received lists of nonadherent patients, specific actions taken by providers NR	2
Hunt et al., 2008[19] NA	Yes	No	No	No	No	No	No	Collaborative care	4
Janson et al., 2003[20] NA	No	No	No	No	No	No	No	NA	4
Janson et al., 2009[21] NA	No	No	No	No	No	No	No	NA	3
Johnson et al., 2006[23] NR	No	No	No	No	No	No	No	NA	5
Johnson et al., 2006[22] NR	No	No	No	No	No	No	No	NA	5
Katon et al., 2001[28] NA Ludman et al., 2003[29] NA Van Korff et al., 2003[30] NA	No	No	Yes	Yes	No	No	No	Shared decision-making regarding maintenance antidepressant treatment	9

Author, Year Trial Name	Facilitation	Contingent Rewards	Motivational Interviewing	Stress Management	Organizational Learning Strategies	Systems Change: Clinical Champions	Systems Change: Total Quality Management/ Continuous Quality Improvement	Other	Number of Components
Katon et al., 1995[24] NA	yes	No	No	No	No	No	No	CBT techniques, training and consultation for PCPs, collaboration between PCP and psychiatrist	6
Katon et al., 1996[25] NA	Yes	No	No	Uncertain	No	No	No	CBT techniques, training and consultation for PCPs, collaboration between PCP and psychiatrist	6
Katon et al., 1999[26] NA Katon et al., 2002[27] NA	Yes	No	No	No	No	No	No	collaborative care with PCP, psychiatrist, and patient	4
Lee et al., 2006[31] FAME	Yes	No	No	No	No	No	No	Blister packaging grouping daily medications	3
Lin et al., 2006[32] NA	Uncertain	No	No	No	No	No	No	NA	2
Maciejewski et al., 2010[33] NA	No	No	No	No	No	No	No	Eliminate copayments for generic medications	1

Author, Year Trial Name	Facilitation	Contingent Rewards	Motivational Interviewing	Stress Management	Organizational Learning Strategies	Systems Change: Clinical Champions	Systems Change: Total Quality Management/ Continuous Quality Improvement	Other	Number of Components
Mann et al., 2010[34] The Statin Choice	No	No	No	No	No	No	No	Decision Aid	3
Montori et al., 2011[35] 2011 NA	No	No	No	No	No	No	No	shared decision-making with provider	3
Murray et al., 2007[36] NA	Yes	No	No	No	No	No	No	NA	3
Nietert et al., 2009[37] NA	Yes	No	No	No	No	No	No	NA	2
Okeke et al., 2009[38] NA	Yes	No	No	No	No	No	No	Visible and audible alarms on dosing aid	2
Pearce et al., 2008[39] Cardiovascular Risk Education and Social Support (CaRESS) Trial	Yes	No	No	No	No	No	No	NA	4
Powell et al., 1995[40] NA	No	No	No	No	No	No	No	NA	1
Powers et al., 2011[68] NA	No	No	No	No	No	No	No	NA	3
Pyne et al., 2011[41] HIV Translating Initiatives for Depression Into Effective Solutions (HITIDES)	Yes	No	No	No	No	No	No	NA	5

Author, Year Trial Name	Facilitation	Contingent Rewards	Motivational Interviewing	Stress Management	Organizational Learning Strategies	Systems Change: Clinical Champions	Systems Change: Total Quality Management/ Continuous Quality Improvement	Other	Number of Components
Rich et al., 1996[42] NA	Yes	No	No	No	No	No	No	NA	5
Rickles et al., 2005[43] NA	Yes	No	No	No	No	No	No	NA	2
Ross et al., 2004[44] NR	No	No	No	No	No	No	No	NA	1
Rudd et al., 2004[45] NA	Yes	No	No	No	No	No	No	NA	6
Rudd et al., 2009[46] NA	Yes	No	No	No	No	No	No	Health literacy	3
Schaffer et al., 2004[47] NA	No	No	No	No	No	No	No	NO	3
Schectman et al., 1994[48] NA	Yes	No	No	No	No	No	No	NA	3
Schneider et al., 2008[49] NA	No	No	No	No	No	uncertain	No	packaging	2
Schnipper et al., 2006[50] NA	yes	No	No	No	No	Uncertain	No	monitoring medication regimens to identify system errors	3
Simon et al., 2006[51] NA	Yes	No	Yes	No	No	No	No	NA	4

Author, Year Trial Name	Facilitation	Contingent Rewards	Motivational Interviewing	Stress Management	Organizational Learning Strategies	Systems Change: Clinical Champions	Systems Change: Total Quality Management/ Continuous Quality Improvement	Other	Number of Components
Sledge et al., 2006[52#2608] NA	yes	No	No	No	No	Uncertain	No	patient-centered approach to case management, comprehensive assessment and report to PCP	2
Smith et al., 2008[53] NR	No	No	No	No	No	No	No	NA	2
Solomon et al., 1998[54] NA Gourley et al., 1998[55] NA	Yes	No	No	No	No	No	No	NA	2
Stacy et al., 2009[56] NA	No	No	No	No	No	No	No	NA	6
Taylor et al., 2003[57] NA	Yes	No	No	No	No	No	No	NA	2
Vivian et al., 2002[58] NA	Yes	No	No	No	No	No	No	NA`	5

Author, Year Trial Name	Facilitation	Contingent Rewards	Motivational Interviewing	Stress Management	Organizational Learning Strategies	Systems Change: Clinical Champions	Systems Change: Total Quality Management/ Continuous Quality Improvement	Other	Number of Components
Waalen et al., 2009[59] NA	Yes	No	No	No	No	No	No	Patients who couldn't afford meds were assisted in obtaining them free from study sponsor (Merck)	4
Wakefield et al., 2011[60] NA	No	No	No	No	No	No	No	NA	2
Weinberger et al., 2002[61] NA	No	No	No	No	No	Yes	No	NA	3
Weymiller et al., 2007[62] Statin Choice Randomized Trial Jones et al., 2009[63] Statin Choice Randomized Trial	No	No	No	No	No	No	No	NA	1
Williams et al., 2010[64] NA	No	No	No	No	No	No	No	Systems change by providing clinician with information about patient adherence	2
Wilson et al., 2010[65] Better Outcomes of Asthma Treatment (BOAT)	Yes	No	Yes	No	No	No	No	NA	6

Author, Year Trial Name	Facilitation	Contingent Rewards	Motivational Interviewing	Stress Management	Organizational Learning Strategies	Systems Change: Clinical Champions	Systems Change: Total Quality Management/ Continuous Quality Improvement	Other	Number of Components
Wolever et al., 2010[66] NA	No	No	Uncertain	No	No	No	No	NA	3
Zhang et al., 2010[67] NA	Uncertain	No	No	Yes	No	No	No	Reduction of out of pocket medication expenses	1

Table D20. Intervention components, part 4

Author, Year Trial Name	Other	Were there direct comparisons between components of interventions?	If yes to previous question, was there a difference between components?	If yes to the previous question, describe the relevant comparisons	Specify differences (results)	Comments
Bender et al., 2010[1] NA	NA	No	No	NA	NA	NA
Berg et al., 1997[2] NA	NA	No	No	NA	NA	NA
Berger et al., 2005[3] NA	NA	No	NA	NA	NA	NA
Bogner et al., 2008[4] NA	No	No	No	NA	NA	NA
Bogner et al., 2010[5] NA	NA	No	No	NA	NA	NA
Bosworth et al., 2005[6] V-STITCH	Patient/provider interaction	No	NA	NA	NA	None
Bosworth et al., 2008[7] TCYB Bosworth et al., 2007[8] TCYB Methods paper	Role of patient provider communication	No	NA	NA	NA	None
Capoccia et al., 2004[9] NA	No	No	No	NA	NA	NA
Carter et al., 2009[10] NA	NA	No	No	NA	NA	None
Chernew et al., 2008[11] NA	NA	No	No	NA	NA	None
Choudhry et al., 2010[12] NA	NA	No	No	NA	NA	None
Choudhry et al., 2011[13] MI FREEE	NA	No	No	NA	NA	
Friedman et al., 1996[14] NA	NA	No	No	NA	NA	It is not clear what type of "counseling" the computer gave to patients to encourage adherence.
Fulmer et al., 1999[15] NA	NA	Yes	No			

Author, Year Trial Name	Other	Were there direct comparisons between components of interventions?	If yes to previous question, was there a difference between components?	If yes to the previous question, describe the relevant comparisons	Specify differences (results)	Comments
Grant et al., 2003[16] NA	NA	Yes	No	NA	NA	compared Questionnaire only to Questionnaire plus education and provider feedback
Guthrie et al., 2001[17] First Myocardial Infarction (MI) Risk Reduction Program	NA	No	NA	NA	NA	None
Hoffman et al., 2003[18] NA	NA	No	No	NA	NA	NA
Hunt et al., 2008[19] NA	NA	No	No	NA	NA	None
Janson et al., 2003[20] NA	NA	No	No	NA	NA	
Janson et al., 2009[21] NA	No	No	No	NA	NA	NA
Johnson et al., 2006[23] NR	NA	No	No	NA	NA	None
Johnson et al., 2006[22] NR	NA	No	No	NA	NA	None
Katon et al., 2001[28] NA Ludman et al., 2003[29] NA Van Korff et al., 2003[30] NA	Depression prevention specialists communicated with PCPs about patients	No	No	NA	NA	NA
Katon et al., 1995[24] NA	NA	No				
Katon et al., 1996[25] NA	NA	No	No	NA	NA	None
Katon et al., 1999[26] NA Katon et al., 2002[27] NA	NA	No	No	NA	NA	

Author, Year Trial Name	Other	Were there direct comparisons between components of interventions?	If yes to previous question, was there a difference between components?	If yes to the previous question, describe the relevant comparisons	Specify differences (results)	Comments
Lee et al., 2006[31] FAME	NA	No	No	NA	NA	None
Lin et al., 2006[32] NA	NA	No	No	NA	NA	None
Maciejewski et al., 2010[33] NA	NA	No	No	NA	NA	None
Mann et al., 2010[34] The Statin Choice	NA	No	No	NA	NA	
Montori et al., 2011[35] NA	role of patient provider communication	no				
Murray et al., 2007[36] NA	NA	No	No	NA	NA	NA
Nietert et al., 2009[37] NA	NA	No	No	NA	NA	None
Okeke et al., 2009[38] NA	NA	No				
Pearce et al., 2008[39] Cardiovascular Risk Education and Social Support (CaRESS) Trial	NA	No	No	NA	NA	NA
Powell et al., 1995[40] NA	NA	No	No	NA	NA	None
Powers et al., 2011[68] NA	NA	No	NA	NA	NA	
Pyne et al., 2011[41] HIV Translating Initiatives for Depression Into Effective Solutions (HITIDES)	NA	No	No	NA	NA	NA
Rich et al., 1996[42] NA	NA	No	NA	NA	NA	None
Rickles et al., 2005[43] NA	NA	No	No	NA	NA	NA
Ross et al., 2004[44] NR	NA	No		NA	NA	None

Author, Year Trial Name	Other	Were there direct comparisons between components of interventions?	If yes to previous question, was there a difference between components?	If yes to the previous question, describe the relevant comparisons	Specify differences (results)	Comments
Rudd et al., 2004[45] NA	NA	No	No	NA	NA	None
Rudd et al., 2009[46] NA						
Schaffer et al., 2004[47] NA	NO	No	No	No	NA	NA
Schectman et al., 1994[48] NA	NA	No	No	NA	NA	None
Schneider et al., 2008[49] NA	NA	No				
Schnipper et al., 2006[50] NA	NA	No				
Simon et al., 2006[51] NA	NA	No	No	NA	NA	
Sledge et al., 2006[52] NA	NA	No				
Smith et al., 2008[53] NR	NA	No		NA	NA	None
Solomon et al., 1998[54] NA Gourley et al., 1998[55] NA	NA	No	No	NA	NA	NA
Stacy et al., 2009[56] NA	NA	No	NA	NA	NA	
Taylor et al., 2003[57] NA	NA	No				
Vivian et al., 2002[58] NA	NA	No	NA	NA	NA	None
Wakefield et al., 2011[60] NA	NA	Yes	No	NA	NA	
Waalen et al., 2009[59] NA	NA	No				

Author, Year Trial Name	Other	Were there direct comparisons between components of interventions?	If yes to previous question, was there a difference between components?	If yes to the previous question, describe the relevant comparisons	Specify differences (results)	Comments
Weinberger et al., 2002[61] NA	yes	No	No	NA	NA	There was a peak flow control group in addition to the control group; the intent of giving that group peak flow meters, instructions on its use, and monitoring calls on PEFR (which the control group did not receive) was to control for the active ingredient of self-monitoring rather than to evaluate the effect of peak flow meters on medication adherence. There were too many differences between the peak flow group and the pharmaceutical care group to evaluate the effect of components.
Weymiller et al., 2007[62] Statin Choice Randomized Trial Jones et al., 2009[63] Statin Choice Randomized Trial	Role of patient provider communication	Yes	Yes	Effect of mode of delivery (i.e., by a clinician during patient visits or by a clinician-researcher before patient visits) on statin adherence at 3 month follow-up, overall	Odds ratio for adherence to statins at 3 month follow-up by mode of delivery (clinician vs. clinician-researcher) OR: 0.895% CI,	None

Author, Year Trial Name	Other	Were there direct comparisons between components of interventions?	If yes to previous question, was there a difference between components?	If yes to the previous question, describe the relevant comparisons	Specify differences (results)	Comments
				acceptability of decision aid, Knowledge Score, & Decisional Conflict Scale score	0.3-2.6 Difference in overall acceptability (clinician vs. clinician-researcher) Odds ratio (OR): 3.1 95% CI, 0.9-11.2 p: 0.08 Adjusted mean difference (AMD): 0.31 95% CI, -0.37-0.98 p: 0.38 Difference in Knowledge Score (out of max 9 points) AMD: 1.6 95% CI, 0.3-2.8p: 0.02 Difference in Decisional Conflict Scale (out of max 100 points) AMD: -6.8 95% CI, -17.6-4.0 p: 0.22	

Author, Year Trial Name	Other	Were there direct comparisons between components of interventions?	If yes to previous question, was there a difference between components?	If yes to the previous question, describe the relevant comparisons	Specify differences (results)	Comments
Williams et al., 2010[64] NA	the intervention supposed to increase communication but the intervention only provided information and did not address communication beyond what provided to UC care group	Yes	No	NA. Also, results described under KQ1	NA	Direct components of the intervention were assessed, because "usual care" included education on adherence. The intervention did not result in a difference in adherence rates because the utilization of the intervention was low. Adherence was better among patients whose physicians viewed adherence data more frequently
Wilson et al., 2010[65] Better Outcomes of Asthma Treatment (BOAT)	Engaging patient to become more involved in their own care through shared decision making	Yes	Yes	Compared two different methods of case management -- SDM and CDM. Results described under KQ1	Differences presented in worksheet 2 for outcomes.	There were 2 intervention arms; responses reflect shared decision making arm
Wolever et al., 2010[66] NA	NA	No	No	NA	NA	NA
Zhang et al., 2010[67] NA	NA	No	No	NA	NA	None

Table D21. Mortality data

Author, Year Trial name	Mortality	Time of measurement	Data source	N	Results
Ross et al., 2004[44] NR	Deaths (%)	NR [only says during study year 2002]	chart review	G1: NR G2: NR	G1: 6 (11%) G2: 6 (11%) 95% CI, NR p: 1.00
Choudhry et al., 2011[13] MI FREEE	Death from cardiovascular causes		Aetna database	G1: 2845 G2: 3010	G1: 1.7 events/100 person years G2: 2.0 events/100 person years 95% CI, NR HR 0.85 (0.60 to 1.21) p: 0.36

Table D22. Morbidity outcomes 1

Author, Year Trial Name	Morbidity Outcome 1	Description of Timing of Measurement of Outcome	Data source	N	Results
Bender et al., 2010[1] NA	Change in Asthma control Test results; higher scores indicate better control of asthma symptoms	at baseline and 10 weeks later at final visit - questions refer to previous 4 weeks	questionnaire; Asthma Control Test (ACT)	G1: 25 G2: 25	G1: 1.120 (3.90) G2: 1.840 (4.14) 95% CI, p: .530
Berg et al., 1997[2] NA	Average symptoms per day (SD) from a journal of daily asthma concerns on wheeze, coughing, shortness of breath, and chest tightness	Symptoms recorded each day for a week at week 7	self-report	G1: 31 G2: 24	G1: 1.1 (0.91) G2: 0.85 (0.93) 95% CI NR P NS
Bogner et al., 2008[4] NA	Center for Epidemiologic Studies-Depression Scale - compared at 6 weeks	interview at baseline and 6 weeks	questionnaire	G1: 32 G2: 32	G1: 9.9 (10.7) G2: 19.3 (15.2) 95% CI, p: .006
Bogner et al., 2010[5] NA	Depressive symptoms	2 times, once at baseline and once at 12 weeks	Center for Epidemiologic Studies Depression Scale (CES-D)	G1: 29 G2: 29	**BL** G1: Mean (SD) = 15.6 (11.7) G2: Mean (SD) = 19.7 (16.7) 95% CI, NR p: 0.47 **EP** G1: Mean (SD) = 9.6 (9.4) G2: Mean (SD) = 16.6 (14.5) 95% CI, NR p: 0.035
Choudhry et al., 2011[13] MI FREEE	fatal or nonfatal vascular event or revascularization	composite of the first readmission for a major vascular event (fatal or nonfatal acute myocardial infarction, unstable angina, stroke, or congestive heart failure) or coronary revascularization (coronary bypass, stenting, or angioplasty)	health claims data	G1: 2845 G2: 3010	G1: 493 patients; 17.6 per 100 person-years G2: 562 patients; 18.8 per 100 person-years Adjusted hazard ratio: 0.93, 95% CI, 0.82-1.04 p: 0.21 Adjusted (for age and baseline coexisting illnesses) hazard ratio: 0.94; 95% CI, 0.83-1.06, p=0.29
Friedman et al., 1996[14] NA	Systolic BP	measured at baseline and at 6-months	BP readings by field technicians	G1: 133 G2: 134	G1: 11 mm Hg (mean decrease) G2: 10.6 mm Hg (mean decrease) 95% CI, NR p: = 0.85

Author, Year Trial Name	Morbidity Outcome 1	Description of Timing of Measurement of Outcome	Data source	N	Results
Fulmer et al., 1999[15] NA	Minnesota Living with Heart Failure Questionnaire (MLHF) score	Measured at baseline, 10 weeks	self-report	G1: 15 G2: 13 G3: 14	**Pre-intervention** mean (SD) G1: 43.1 (20.8) G2: 54.4 (21.1) G3: 46.6 (27.7) **Post-intervention** mean (SD) G1: 36.7 (19.9) G2: 32.9 (25.2) G3: 32.9 (22.9) 95% CI, NR p: NR "There was improvement in MLHF scores [for the sample] (p<0.001)… Group membership did not make a difference..."
Janson et al., 2003[20] NA	Symptom severity at week 7; between group difference in change from baseline to final visit at week 7 (95% CI)	recorded daily, averaged over a week	questionnaire	G1: 33 G2: 32	G1: 8(7) G2: 7 (6) between group change: -0.9 (-4 to 2) p= 0.56
Janson et al., 2009[21] NA	mean change of FEV1 % predicted (before bronchodilator): During intervention(T0-T1), following intervention (T1-T2), and for entire study duration (T0-T2)	measured at t0, t1, t2; between t1 and t2 constitutes 14 weeks apart; not clear but appears that represents single measurement for time period	electronic peak flow meter	G1: 45 G2: 39	**T0-T1** G1: 1.47 G2: 2.72 p: 0.32 **T1-T2** G1: 1.13 G2: -0.37 p: .25 **T0-T2** G1: 2.60 G2: 1.13 p: 0.25

Author, Year Trial Name	Morbidity Outcome 1	Description of Timing of Measurement of Outcome	Data source	N	Results
Katon et al., 1995[24] NA	% patients whose scores on SCL-20 improved ≥50%	4-month follow-up for bivariate; 1m, 4m and 7m for multivariate and group-by-time interaction	Self-report	**Major depression group** N=91 **Minor depression group** N=126	**Bivariate:** **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** **Major depression group** G1: NR G2: NR 95% CI, NR p: <0.005 **Minor depression group** G1: NR G2: NR 95% CI, NR p: not significant **Group-by-time** **Major depression group** G1: NR G2: NR 95% CI, NR p: <0.004

Author, Year Trial Name	Morbidity Outcome 1	Description of Timing of Measurement of Outcome	Data source	N	Results
Katon et al., 1996[25] NA	Meeting criteria for depression	baseline, 1, 4, and 7 months	DSM-III-R diagnostic manual	NR	**Major Depression Group at 4-month follow up** (% meeting criteria for major depression) G1: 7.4% G2: 23.1% p= NR (% meeting criteria for minor depression) G1: 33.8% G2: 30.8% p= NR **Minor Depression Group at 4-month follow up** (% meeting criteria for minor depression) G1: 25.6% G2: 33.3% p= NR
Katon et al., 1999[26] NA Katon et al., 2002[27] NA	Rate of change in depression severity; after controlling for age, sex, and chronic disease score (Reported in 9123)	Measured at 3 and 6 months	self-reporting on SCL-20 questionnaire	NR	**At 3 months**: F(1,186): 12.38 p: 0.001 **At 6 months**: F(1,185): 3.09 p: 0.08

Author, Year Trial Name	Morbidity Outcome 1	Description of Timing of Measurement of Outcome	Data source	N	Results
Katon et al., 2001[28] NA Ludman et al., 2003[29] NA Van Korff et al., 2003[30] NA	Depression severity (Katon et al., Van Korff et al.)	Timeframe: one month; measured at 3, 6, 9, 12 months.	SCL Depression scale (0 to 4), self-report	BL G1: 194 G2: 192 Other Ns NR	**Across 12 months**: Mean difference: 0.08 p: 0.04 **BL** mean (SD) G1: 0.83 (0.39) G2: 0.84 (0.35) 95% CI, NR p: NR **3 mos** G1: 0.75 (0.55) G2: 0.79 (0.47) 95% CI, NR p: NR *Sig difference between 2 depression specialists **6 mos** G1: 0.74 (0.54) G2: 0.78 (0.51) 95% CI, NR p: NR **9 mos** G1: 0.69 (0.56) G2: 0.86 (0.57) 95% CI, NR p: NR **12 m**os G1: 0.65 (0.51) G2: 0.74 (0.54) 95% CI, NR p: NR

Author, Year Trial Name	Morbidity Outcome 1	Description of Timing of Measurement of Outcome	Data source	N	Results
Lin et al., 2006[32] NA	A1C	Measured only once at baseline (endpoint data possibly reported in other report from same study, Source 24)	NR	**BL** G1: 164 G2: 165 **EP** G1: 164 G2: 165	**BL** (%) G1: Mean (SD) = 8.0% (1.6%) G2: Mean (SD) = 8.0% (1.5%) 95% CI, NR p: NR **EP** G1: NR G2: NR 95% CI, NR p: NR
Okeke et al., 2009[38] NA	Intraocular pressure	Measured 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)	Applanation	G1: NR G2: NR	G1: NR G2: NR 95% CI, NR p: 0.81
Pearce et al., 2008[39] Cardiovascular Risk Education and Social Support (CaRESS) Trial	A1C	3 times, at baseline (visit 2), visit 4, and visit 6 over a 12-month period	Phlebotomy during study practice site visits	**BL** G1 + G2: 106 G3: 85 Midpoint (6 months) G1 + G2: 87 G3: 63 **EP** (9-12 months) G1 + G2: 74 G3: 63	**BL** (%) G1 + G2: 7.5 G3: 7.6 95% CI, NR p (G1 + G2 vs. G3): 0.4102 (unadjusted), NR (adjusted) Midpoint (%) G1 + G2: 8.3 G3: 7.8 p (G1 + G2 vs. G3): 0.0567 (unadjusted), 0.0429 (adjusted for multiple factors, including baseline outcome values **EP** (%) G1 + G2: 7.4 G3: 7.4 p (G1 + G2 vs. G3): 0.6440 (unadjusted), 0.9164 (adjusted)
Rudd et al., 2004[45] NA	Change in systolic BP between baseline and 6 months (measured at clinic)	Measured at baseline and at 6 months	Clinic measurement by blinded study personnel	G1: 74 G2: 76	G1: -14.2 (95% CI -18.1, -10.0) G2:-5.7 (95% CI -10.2, -1.3) p<0.01

Author, Year Trial Name	Morbidity Outcome 1	Description of Timing of Measurement of Outcome	Data source	N	Results
Schaffer et al., 2004[47] NA	ACQ (lower=better): mean (SD)	baseline, 3, 6 months; timeframe: specific to time of measurement	questionnaire	G1: 11 G2: 10 G3:12 G4:13	G1(audio+ book) Pre: 1.50 (0.56) 3 mo: 1.10 (0.58) 6 mo: 1.30 (0.76) G2(audio only) Pre: 1.84 (1.05) 3 mo: 1.62 (1.04) 6 mo: 1.47 (1.14) G3(book only) : Pre: 1.42 (0.82) 3 mo: 1.39 (1.0) 6 mo: 1.30 (0.76) G4(UC) : Pre: 1.72 (1.22) 3 mo: 1.71 (1.18) 6 mo: 1.25 (1.07) Pre-3: G4 vs. G2 p = .6 G4 vs. G1 p = .8 G4 vs. G1 p = .1 Pre-6 G4 vs. G3 p = .5 G4 vs. G2 p = .4 G4 vs. G3 p = .8

Author, Year Trial Name	Morbidity Outcome 1	Description of Timing of Measurement of Outcome	Data source	N	Results
Schneider et al., 2008[49] NA	Absolute change in Bp: DBP	6 and 12 months	Medical chart review	G1: 47 G2: 38	Mean (SD) absolute change 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
Solomon et al., 1998[54] NA Gourley et al., 1998[55] NA	Hypertension group: Problems with sexual functioning during previous 4 weeks, n (%) (Item 2)	Visit 1: Baseline Visit 5: 4-6 months	Hypertension/Lipid Form 5.1 developed by The Health Outcomes Institute	Overall N: 63 G1: NR G2: NR	Visit 1 G1: 22 (34.0%) G2: 19 (26.0%) 95% CI, NR p: NR Visit 5 G1: 8 (2.5%) G2: 8 (25.0%) 95% CI, NR p: NR p=0.003 for difference in sexual functioning from visit 1 to visit 5 in treatment group
Wilson et al., 2010[65] Better Outcomes of Asthma Treatment (BOAT)	Lung function (FEV1%)	follow-up year 1, measured once	Spirometry	G1: 165 G2: 170 G2: 172	G1: 76.5% G3: 73.1% p= 0.0068 G1: 76.5% G2: 75.8% p: 0.47 G2: 75.8 G3: 73.1% p: .0457

Author, Year Trial Name	Morbidity Outcome 1	Description of Timing of Measurement of Outcome	Data source	N	Results
Wolever et al., 2010[66] NA	Hemoglobin A1C (all)	Twice within a 6-month period	Blood work	G1: 27 G2: 22	G1: BL Mean (SD) = 7.9 (1.98), EP Mean (SD) = 7.5 (1.76) G2: BL Mean (SD) = 8.1 (1.92), EP Mean (SD) = 8.2 (1.92) 95% CI, NR p: Within-group change from baseline NS, between-group change NR

Table D23. Morbidity outcomes 2

Author, Year Trial Name	Morbidity Outcome 2	Description of Timing of Measurement of Outcome	Data source	N	Results
Bender et al., 2010[1] NA	NA	NA	NA	NA	NA
Berg et al., 1997[2] NA	Percent symptom-free days (SD) from a journal of daily asthma concerns on wheeze, coughing, shortness of breath, and chest tightness	Symptoms recorded each day for a week at week 7	self-report	G1: 31 G2: 24	G1: 44 (38) G2: 60 (37) 95% CI NR P<0.1
Bogner et al., 2008[4] NA	Systolic BP, mean (SD), mm Hg - compared at 6 weeks	measured at baseline and at 6 weeks	automated BP monitor	G1: 32 G2: 32	G1: 127.3 (17.7) G2: 141.3 (18.8) 95% CI, p: .003
Bogner et al., 2010[5] NA	A1C/Blood glycemic control	2 times, at BL and 12 weeks	A1C assays	G1: 29 G2: 29	**BL** (%) G1: Mean (SD) = 7.3 (2.3) G2: Mean (SD) = 7.3 (2.0) 95% CI, NR p: 0.70 **EP** (%) G1: Mean (SD) = 6.7 (2.3) G2: Mean (SD) = 7.9 (2.6) 95% CI, NR p: 0.019
Choudhry et al., 2011[13] MI FREEE	rate of total major vascular events or revascularization	allowing for the occurrence of more than one event per patient and the time to the first major vascular event (i.e., the primary composite outcome excluding revascularization)	health claims data	G1: 2845 G2: 3010	G1: 622 patients; 21.5 per 100 person-years G2: 729 patients; 23.3 per 100 person-years Adjusted hazard ratio: 0.89, 95% CI, 0.80-0.99 p: 0.03
Friedman et al., 1996[14] NA	Diastolic BP	measured at baseline and at 6-months	BP readings by field technicians	G1: 133 G2: 134	G1: 5.4 mm Hg (mean decrease) G2: 3.3 mm Hg (mean decrease) 95% CI, NR p: =0.09

Author, Year Trial Name	Morbidity Outcome 2	Description of Timing of Measurement of Outcome	Data source	N	Results
Fulmer et al., 1999[15] NA	SF-36 score	Measured at baseline, 10 weeks	self-report	G1: 15 G2: 13 G3: 14	Pre-intervention mean (SD) G1: 86.1 (17.0) G2: 81.0 (15.2) G3: 87.3 (24.3) Post-intervention mean (SD) G1: 85.9 (18.9) G2: 90.1 (20.6) G3: 91.7 (22.7) 95% CI, NR p: NR "There was no significant change in the SF-36 scores for the sample…. Group membership did not make a difference..."
Janson et al., 2003[20] NA	FEV1 (% predicted) at week 7; between group difference in change from baseline to final visit at week 7 (95% CI)	recorded at every visit	questionnaire	G1: 33 G2: 32	G1: 90 (16) G2: 80 (20) Between group difference: 5 (-1 to 10) p = 0.09

Author, Year Trial Name	Morbidity Outcome 2	Description of Timing of Measurement of Outcome	Data source	N	Results
Janson et al., 2009[21] NA	mean change Symptom Score; During intervention(T0-T1), following intervention (T1-T2), and for entire study duration (T0-T2) Symptom-free days (symptom score =0)	"rated daily by participants; scores averaged weekly for analysis"	rated in subject maintained diaries; 0-10 scale	G1: 45 G2: 39	Mean change: T0-T1 G1: -1.28 G2: -1.41 p: 0.84 T1-T2 G1: -0.97 G2: 0.11 95% CI, p: .06 T0-T2 G1: -2.25 G2: -1.30 p: 0.19 Symptom-free days Odds Ratios T0-T1 G1: 2.2 G2:1.6 p: 0.48 T1-T2: G1: 2.7 G2: 1.8 p: .63 T0-T2: G1: 5.9 G2: 2.8 p: 0.51

Author, Year Trial Name	Morbidity Outcome 2	Description of Timing of Measurement of Outcome	Data source	N	Results
Katon et al., 1995[24] NA	% patients whose scores on IDS improved ≥50%	4-month follow-up for bivariate; 1m, 4m and 7m for multivariate and group-by-time interaction	other (specify): clinician-rated	**Major depression group** N=91 **Minor depression group** N=126	**Bivariate:** **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** **Major depression group** G1: NR G2: NR 95% CI, NR p: <0.02 **Minor depression group** G1: NR G2: NR 95% CI, NR p: not significant **Group-by-time** **Major depression group** G1: NR G2: NR 95% CI, NR p: NR, but statistically significant

Author, Year Trial Name	Morbidity Outcome 2	Description of Timing of Measurement of Outcome	Data source	N	Results
Katon et al., 1996[25] NA	50% or more Improvement on the SCL-20 depression scale	4-month follow up	SCL-20 scale	G1: 77 G2: 76	Major Depression Group (% showing ≥50% improvement) G1: 70.4% G2: 42.3% p:0.04 NS difference between G1 and G2 in the minor depression group G1: 66.7% G2: 52.8% p: 0.22
Katon et al., 1999[26] NA Katon et al., 2002[27] NA	Percentage of patients who were asymptomatic (DSM-IV of 0 or 1) (Reported in 9123)	Measured at 3 and 6 months	Structured clinical interview for DSM-IV symptoms	NR	**At 3 mos**. G1: 40% G2: 23% Chi-square: 6.18 p: 0.01 **At 6 mos**. G1: 44% G2: 31% Chi-square: 3.90 p: 0.05

Author, Year Trial Name	Morbidity Outcome 2	Description of Timing of Measurement of Outcome	Data source	N	Results
Katon et al., 2001[28] NA	Functional impairment, Disability (Von Korff et al.)	BL, 3, 6, 9, 12 months.	Sheehan Disability Scale, self-report	**BL** G1: 194 G2: 192 **3 mos** G1: 182 G2: 181 **6 mos** G1: 172 G2: 167 **9 mos** G1: 156 G2: 145 **12 mos** G1: 121 G2: 111	**3 mos** mean (SD) G1: 2.79 (3.94) G2: 2.08 (2.07) 95% CI, NR p: NR **6 mos** mean (SD) G1: 2.41 (3.23) G2: 2.23 (2.22) 95% CI, NR p: NR **9 mos** mean (SD) G1: 2.30 (2.06) G2: 2.30 (2.28) 95% CI, NR p: NR **12 mos** mean (SD) G1: 2.09 (1.98) G2: 2.08 (2.07) 95% CI, NR p: NR Effects: Intervention Estimate: 0.15 (0.17) T-statistic: 0.86 p: 0.39 Time Estimate: -0.06 (0.06) T-statistic: 1.06 p: 0.29 Intervention x time Estimate: -0.12 (0.08) T-statistic: 1.47 p: 0.14
Ludman et al., 2003[29] NA					
Van Korff et al., 2003[30] NA					

Author, Year Trial Name	Morbidity Outcome 2	Description of Timing of Measurement of Outcome	Data source	N	Results
Lin et al., 2006[32] NA	BMI	Measured 2 times, once at baseline and once at endpoint	NR	**BL** G1: 164 G2: 165 **EP** G1: 164 G2: 165	**BL** (kg/m^2) (Mean (SD)) G1: 33.9 (8.6) G2: 36.3 (11.1) 95% CI, NR p: ≤0.05 without adjustment **EP** (kg/m^2) G1: 33.0 (7.9) G2: 36.1 (10.0) 95% CI, NR p: ≤0.01 with adjustment
Pearce et al., 2008[39] Cardiovascular Risk Education and Social Support (CaRESS) Trial	Mean systolic BP	7 times over a 12-month period	Standardized BP readings, following American Heart Association guidelines	**BL** G1 + G2: 108 G3: 91 **Midpoint:** G1 + G2: 92 G3: 74 **EP** G1 + G2: 81 G3: 60	**BL**(mmHg) G1 + G2: 141.3 G3: 139.0 95% CI, NR p (G1 + G2 vs. G3): 0.5433 (unadjusted), NR (adjusted) **Midpoint** (mmHg) G1 + G2: 135.5 G3: 133.6 95% CI, NR p (G1 + G2 vs. G3): 0.3836 (unadjusted), 0.4969 (adjusted) **EP**(mmHg) G1 + G2: 134.0 G3: 133.8 95% CI, NR p (G1 + G2 vs. G3): 0.9427 (unadjusted), 0.6475 (adjusted)
Rudd et al., 2004[45] NA	Change in diastolic BP between baseline and 6 months	Measured at baseline and at 6 months	Clinic measurement by blinded study personnel	G1: 74 G2: 76	G1: -6.5 (95% CI -8.8, -4.1) G2:-3.4 (95% CI -5.3, -1.5) p<0.05

Author, Year Trial Name	Morbidity Outcome 2	Description of Timing of Measurement of Outcome	Data source	N	Results
Schaffer et al., 2004[47] NA	AQLQ mean (SD)	baseline, 3, 6 months; timeframe: specific to time of measurement	questionnaire	G1: 11 G2: 10 G3:12 G4:13	AQLQ mean (SD) G1 Pre: 4.97 (0.88) 3 mos: 5.15 (0.91) 6 mos: 5.22 (0.99) G2 Pre: 4.60 (1.1) 3 mos: 4.94 (0.97) 6 mos: 5.30 (0.8) G3: Pre: 4.71 (1.16) 3 mo: 5.13 (1.32) 6 mo: 5.22 (0.98) G4 : Pre: 4.65 (1.23) 3 mo: 4.68 (1.49) 6 mo: 4.87 (1.2) Pre-3: G4 vs.G2 p = .5 G4 vs. G1 p = .3 G4 vs. G3 p = .6 Pre-6 G4 vs. G3 p = .2 G4 vs. G2 p = .4 G4 vs. G1 p = .8

Author, Year Trial Name	Morbidity Outcome 2	Description of Timing of Measurement of Outcome	Data source	N	Results
Schneider et al., 2008[49] NA	Absolute Change in Bp: SBP	6 and 12 months	Medical chart review	G1: 47 G2: 38	Mean (SD) absolute change **6 mos** G1: -4.2 (21.5) G2: -4.2 (20.9) 95% CI, NR p: 0.992 **12 mos** G1: -2.7 (16.5) G2: -1.3 (17.8) 95% CI, NR p: 0.669
Solomon et al., 1998[54] NA Gourley et al., 1998[55] NA	Hypertension group reporting "Feeling dizzy upon standing up, " mean (SD) (Item 8)	Visit 1: Baseline Visit 5: 4-6 months	Hypertension/Lipid Form 5.1 developed by The Health Outcomes Institute; Likert scale of 1 (never) to 5 (very often);	Overall N: 63 G1: NR G2: NR	**Visit 1** G1: 1.7 (1.1) G2: 2.0 (1.1) 95% CI, NR p: NR **Visit 5** G1: 1.4 (0.8) G2:1.4 (0.8) 95% CI, NR p: NR
Wilson et al., 2010[65] Better Outcomes of Asthma Treatment (BOAT)	FEV1:FEV6 ratio	follow-up year 1, measured once	Spirometry	G1: 165 G2: 170 G2: 172	G1: 72.8% G3:70.0% p= 0.0005 G1: 72.8% G2: 71.8% p: 0.09 G2: 71.8% G3: 70.0% p: 0.07

Author, Year Trial Name	Morbidity Outcome 2	Description of Timing of Measurement of Outcome	Data source	N	Results
Wolever et al., 2010[66] NA	Hemoglobin A1C (patients with A1C > 7% at baseline)	Twice within a 6-month period	Blood work	G1: 16 G2: NR	G1: **BL** mean (SD) = 8.9 (1.78), **EP** mean (SD) = 8.3 (1.76) G2: **BL** mean (SD) = 8.8 (1.95), **EP** mean (SD) = 8.8 (1.99) 95% CI, NR p: G1 - Within-group change from baseline = 0.030

Table D24. Morbidity outcomes 3

Author, Year Trial Name	Morbidity Outcome 3	Description of Timing of Measurement of Outcome	Data source	N	Results
Bogner et al., 2008[4] NA	Diastolic BP, mean (SD), mm Hg - compared at 6 weeks	measured at baseline and at 6 weeks	automated BP monitor	G1: 32 G2: 32	G1: 75.8 (10.7) G2: 85.0 (11.9) 95% CI, p: .002
Choudhry et al., 2011[13] MI FREEE	First fatal or nonfatal vascular event	NA	health claims data	G1: 2845 G2: 3010	G1: 329 patients; 11.0 per 100 person-years G2: 405 patients; 12.8 per 100 person-years Adjusted hazard ratio: 0.86, 95% CI, 0.74-0.99 p: 0.03
Janson et al., 2003[20] NA	Perceived control of asthma at week 7; between group difference in change from baseline to final visit at week 7 (95% CI)	timeframe of measure not reported; measured at each study visit	questionnaire	G1: 33 G2: 32	G1: 42 (5) G2: 42 (5) Between group difference: 2.6 (0.1 to 5), p= 0.04

Author, Year Trial Name	Morbidity Outcome 3	Description of Timing of Measurement of Outcome	Data source	N	Results
Janson et al., 2009[21] NA	Mean change Eosinophil cationic protein (ECP) (nanograms/mL); Eosinophils > 0% (> 1/500 cells), During intervention(T0-T1), following intervention (T1-T2), and for entire study duration (T0-T2)	collected once at the end of each time period; During intervention(T0-T1), following intervention (T1-T2), and for entire study duration (T0-T2)	sputum sample	G1: 45 G2: 39	**T0-T1** G1: 0.88 G2: 1.05 p: 0.55 **T1-T2** G1: 0.88 G2: 1.11 95% CI, p: .44 **T0-T2** G1: 0.77 G2: 1.17 p: 0.18 Odds Ratios of >0% ECP **T0-T1**: G1: 0.5 G2: 1.0 p: 0.4 **T1-T2**: G1: 3.1 G2: 0.6 p: 0.09 **T0-T2:** G1: 1.7 G2: 0.6 p: 0.29

Author, Year Trial Name	Morbidity Outcome 3	Description of Timing of Measurement of Outcome	Data source	N	Results
Katon et al., 2001[28] NA Ludman et al., 2003[29] NA Van Korff et al., 2003[30] NA	Functional impairment (Von Korff et al.)	BL, 3, 6, 9, 12 months	Self-report, SF-36 Social functioning Scale(using imputed data and adjusting for age, sex, chronic disease score, neuroticism, and baseline SCL)	**BL** G1: 194 G2: 192 **3 mos** G1: 186 G2: 186 **6 mos** G1: 181 G2: 170 **9 mos** G1: 175 G2: 164 **12 mos** G1: 174 G2: 153	**3 mos** mean (SD) G1: 81.4 (20.5) G2: 81.1 (21.1) 95% CI, NR p: NR **6 mos** mean (SD) G1: 83.3 (20.2) G2: 83.0 (20.9) 95% CI, NR p: NR **9 mos** mean (SD) G1: 84.7 (19.7) G2: 81.4 (22.4) 95% CI, NR p: NR **12 mos** mean (SD) G1: 86.9 (17.8) G2: 81.7 (20.4) 95% CI, NR p: NR Effects: Intervention Estimate: 0.27 (1.42) T-statistic: 0.19 p: 0.85 Time Estimate: 0.66 (0.48) T-statistic: 1.38 p: 0.17 Intervention x time Estimate: 1.31 (0.66) T-statistic: 1.98 p: 0.047

Author, Year Trial Name	Morbidity Outcome 3	Description of Timing of Measurement of Outcome	Data source	N	Results
Katon et al., 1996[25] NA	50% or more improvement on IDS	4-month follow up	IDS	G1: 77 G2: 76	Major Depression Group (% showing ≥50% improvement) G1: 74.1% G2: 42.3%p:0.02 No significant differences between G1 and G2 in the minor depression group G1: 51.3% G2: 52.8% p: 0.90
Lin et al., 2006[32] NA	Adjusted mean BMI difference (baseline minus endpoint)	NA	NR	**BL** G1: 164 G2: 165 **EP** G1: 164 G2: 165	**BL** (kg/m^2) = NA 95% CI, NA p: NA **EP** (kg/m^2) = 0.70 95% CI, 0.17 to 1.24 p: ≤0.01 with adjustment
Pearce et al., 2008[39] Cardiovascular Risk Education and Social Support (CaRESS) Trial	Mean LDL cholesterol level	6 times over a 12-month period	Phlebotomy during study practice site visits	BL G1 + G2: 24 G3: 16 Midpoint G1 + G2: 18 G3: 11 Endpoint G1 + G2: 18 G3: 11	**BL** G1 + G2: 137.0 G3: 137.3 95% CI, NR p (G1 + G2 vs. G3): 0.9471 (unadjusted), NA (adjusted) **Midpoint** G1 + G2: 139.4 G3: 130.5 95% CI, NR p (G1 + G2 vs. G3): 0.6716 (unadjusted), NA (adjusted) **EP** G1 + G2: 135.4 G3: 110.6 95% CI, NR p (G1 + G2 vs. G3): 0.3238 (unadjusted), NA (adjusted)

Author, Year Trial Name	Morbidity Outcome 3	Description of Timing of Measurement of Outcome	Data source	N	Results
Schaffer et al., 2004[47] NA	PQAQ(higher=better): mean	baseline, 3, 6 months; timeframe: specific to time of measurement	questionnaire	G1: 11 G2: 10 G3: 12 G4: 13	G1: Pre: 43.72 (5.14) 3 mo: 49.90 (4.6) 6 mo: 43.33 (14.43) G2: Pre: 42.70 (6.696) 3 mo: 44.0 (4.97) 6 mo: 44.20 (6.16) G3 :Pre: 44.50 (4.62) 3 mo: 45.75 (6.27) 6 mo: 43.33 (14.44) G4:Pre: 44.61 (6.47) 3 mo: 44.67 (6.82) 6 mo: 45.27 (5.57) Pre-3: G4 vs. G2 p = .8 G4 vs. G1 p = .6 G4 vs. G3 p = .3 Pre-6 G4 vs. G3 p = .2 G4 vs. G2 p = .4 G4 vs. G1 p = .8
Schneider et al., 2008[49] NA	Occurrence of angina	6 and 12 months for the past 6 months	Medical chart review	G1: 47 G2: 38	G1: NR G2: NR 95% CI, NR p: NR Numbers not reported, but results were not significant
Wilson et al., 2010[65] Better Outcomes of Asthma Treatment (BOAT	Change in Asthma control;	measured baseline and at FU year 1; measured for the preceding 4 weeks and reported as change in ATAQ score	Asthma Therapy Assessment Questionnaire (ATAQ); 4-item scale.	G1: 182 G2: 180 G3: 189	Change in ATAQ score G1: -.80 G2: -.54 G3: -.46 ATAQ =0 (no asthma control problems) G1:G3 OR: 1.9 95% CI, 1.3-2.9 p-0.002 G2:G3 OR: 1.6 95% CI, 1.1-2.4 p=0.0239

Table D25. Morbidity outcomes 4

Author, Year Trial Name	Morbidity Outcome 4	Description of Timing of Measurement of Outcome	Data source	N	Results
Janson et al., 2003[20] NA	Eosinophils cationic protein at week 7; between group difference in change from baseline to final visit at week 7 (95% CI)	collected at week 1, week 2, and week 7	sputum sample	G1: 29 G2: 29	G1: 231 (203) G2: 324 (346) Between group difference: -72 (-8 to 63), p= 0.29
Janson et al., 2009[21] NA	Tryptase > 1 microgram/L Percentage of neutrophil counts	collected once at the end of each time period; During intervention(T0-T1), following intervention (T1-T2), and for entire study duration (T0-T2)	sputum sample	NA	Tryptase>1 microgram/L; Odds ratio T0-T1: G1: 0.1 G2: 0.2 p: 0.29 T1-T2: G1: 0.1 G2: 0.4 p: 0.24 T0-T2: G1: 0.0 G2: 0.1 p: 0.08 Mean change in neutrophil % T0-T1: G1: 2.7 G2:: -1.7 p: 0.41 T1-T2: G1: 2.6 G2. -5.2 p: 0.18 T0-T2: G1: 5.3 G2: -6.7 p: 0.04

Author, Year Trial Name	Morbidity Outcome 4	Description of Timing of Measurement of Outcome	Data source	N	Results
Katon et al., 2001[28] NA Ludman et al., 2003[29] NA Van Korff et al., 2003[30] NA	Functional impairment (Von Korff et al.)	BL, 3, 6, 9, 12 months	Self-report , SF-36 Role-Emotional Scale(using imputed data and adjusting for age, sex, chronic disease score, neuroticism, and baseline SCL)	**BL** G1: 194 G2: 192 **3 mos** G1: 186 G2: 186 **6 mos** G1: 181 G2: 170 **9 mos** G1: 175 G2: 164 **12 mos** G1: 174 G2: 153	**3 mos** mean (SD) G1: 67.2 (35.6) G2: 68.3 (35.6) 95% CI, NR p: NR **6mos** mean (SD) G1: 67.8 (36.5) G2: 72.1 (31.8) 95% CI, NR p: NR **9mos** mean (SD) G1: 70.8 (36.3) G2: 71.0 (34.3) 95% CI, NR p: NR **12mos** mean (SD) G1: 75.9 (32.2) G2: 73.9 (36.2) 95% CI, NR p: NR Effects: Intervention Estimate: -1.52 (2.21) T-statistic: 0.69 p: 0.49 Time Estimate: 2.51 (0.88) T-statistic: 2.86 p: 0.004 Intervention x time Estimate: 0.32 (1.16) T-statistic: 0.28 p: 0.78

Author, Year Trial Name	Morbidity Outcome 4	Description of Timing of Measurement of Outcome	Data source	N	Results
Pearce et al., 2008[39] Cardiovascular Risk Education and Social Support (CaRESS) Trial	SF-36 Physical composite score	3 times over a 12-month period, at baseline, visit 5, and endpoint	SF-36 Health Survey	**BL** G1 + G2: 107 G3: 88 **Midpoint** G1 + G2: 84 G3: 74 **EP** G1 + G2: 74 G3: 72	**BL** G1 + G2: 38.0 G3: 40.9 95% CI, NR p: 0.0829 (unadjusted), NA (adjusted) **Midpoint** G1 + G2: 42.7 G3: 42.6 95% CI, NR p: 0.4145 (unadjusted), 0.9598 (adjusted) **EP** G1 + G2: 41.4 G3: 41.6 95% CI, NR p: 0.4345 (unadjusted), 0.9056 (adjusted)
Schneider et al., 2008[49] NA	Occurrence of MI	6 and 12 months for the past 6 months	Medical chart review	G1: 47 G2: 38	G1: NR G2: NR 95% CI, NR p: NR Numbers not reported, but results were not significant

Table D26. Morbidity outcomes 5

Author, Year Trial Name	Morbidity Outcome 5	Description of Timing of Measurement of Outcome	Data source	N	Results
Janson et al., 2003[20] NA	Tryptase at week 7; between group difference in change from baseline to final visit at week 7 (95% CI)	collected at week 1, week 2, and week 7	Sputum sample	G1: 31 G2: 31	G1: 5 (9) G2: 3 (5) Between group differences: - 4(- 9 to 2), p= 0.17
Janson et al., 2009[21] NA	Frequency of nighttime awakenings	"rated daily by participants; scores averaged weekly for analysis"	rated in subject-maintained diaries	G1: 45 G2: 39	Odds ratios **T0-T1**: G1: 0.2 G2: 0.7 p: 0.13 **T1-T2**: G1: 0.7 G2: 1.2 p: 0.45 **T0-T2**: G1: 0.2 G2: 0.8 p: 0.03
Pearce et al., 2008[39] Cardiovascular Risk Education and Social Support (CaRESS) Trial	SF-36 Mental composite score	3 times over a 12-month period, at baseline, visit 5, and endpoint	SF-36 Health Survey	**BL** G1 + G2: 107 G3: 88 **Midpt** G1 + G2: 84 G3: 74 **EP** G1 + G2: 74 G3: 72	**BL** G1 + G2: 46.8 G3: 46.8 95% CI, NR p: 0.9779 (unadjusted), NA (adjusted) **Midpoint** G1 + G2: 42.7 G3: 40.1 95% CI, NR p: 0.2666 (unadjusted), 0.2187 (adjusted) **EP** G1 + G2: 45.7 G3: 47.9 95% CI, NR p: 0.5200 (unadjusted), 0.2916 (adjusted)

Author, Year Trial Name	Morbidity Outcome 5	Description of Timing of Measurement of Outcome	Data source	N	Results
Schneider et al., 2008[49] N-A	Occurrence of stroke	6 and 12 months for the past 6 months	Medical chart review	G1: 47 G2: 38	G1: NR G2: NR 95% CI, NR p: NR Numbers not reported, but results were not significant

Table D27. Morbidity outcomes 6

Author, Year Trial Name	Morbidity Outcome 6	Description of Timing of Measurement of Outcome	Data source	N	Results
Janson et al., 2003[20] NA	Eosinophils (%) at week 7; between group difference in change from baseline to final visit at week 7 (95% CI)	collected at week 1, week 2, and week 7	Sputum sample	G1: 33 G2: 32	G1: 2 (2) G2: 7 (12) Between group differences: -5 (-8 to -1), p= 0.02
Schneider et al., 2008[49] N-A	Reduced BP – DBP	6 and 12 months	Medical chart review	G1: 47 G2: 38	% of patients with reduced BP (DBP) **At 6 months**: G1: 46.7 G2: 37.1 **At 12 months**: G1: 48.0 G2: 18.2 p= 0.031

Table D28. Morbidity outcome 7

Author, Year Trial Name	Morbidity Outcome 7	Description of Timing of Measurement of Outcome	Data source	N	Results
Janson et al., 2003[20] NA	Eosinophils (%) at week 7; between group difference in change from baseline to final visit at week 7 (95% CI)	collected at week 1, week 2, and week 7	Sputum sample	G1: 33 G2: 32	G1: 2 (2) G2: 7 (12) Between group differences: -5 (-8 to -1), p= 0.02
Schneider et al., 2008[49] NA	Reduced BP - SBP	6 and 12 months	Medical chart review	G1: 47 G2: 38	% of patients with reduced BP (SBP) At 6 months: G1: 48.9 G2: 62.9 At 12 months: G1: 46.0 G2: 40.9

Table D29. Patient satisfaction outcomes 1

Author, Year Trial Name	Patient satisfaction 1	Description of Timing of Measurement of Outcome	Data source	N	Results
Katon et al., 1995[24] NA	% of patients rating quality of depression care as good to excellent	baseline, 4 months	self-report	**Major depression group** N=91 **Minor depression group** N=126	**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[25] NA	% Rating the quality of care good or excellent	4-month follow up	questionnaire		**Major Depression Group** G1: 88.5% G2: 56% p: <0.009 **Minor Depression Group** G1: 97.1% G2: 71.4% p: 0.003
Katon et al., 1999[26] NA Katon et al., 2002[27] NA	Percent of patients who rated quality of care received for depression as good to excellent (Reported in Katon et al., 1999)	Measured at 3 mos, 6 mos.	Self-report	NR	**At 3 mos**: G1: 94.5% G2: 63.9% Chi-square: 23.51 P<0.00001 **At 6 mos**: G1: 79.5% G2: 63.5% Chi-square: 4.21 p: 0.04
Mann et al., 2010[34] The Statin Choice	Decisional Conflict Scale--Informed subscale, with lower scores representing less conflict	Immediately after intervention and control	self-report	G1: NR G2: NR	G1: 27.1 G2: 33.8 95% CI, NR p: 0.02

Author, Year Trial Name	Patient satisfaction 1	Description of Timing of Measurement of Outcome	Data source	N	Results
Montori et al., 2011[35]	Mean satisfaction with knowledge transfer	NR	Self-report	G1: NR G2: NR	Amount of information G1: 6.6 G2: 6.3 95% CI, NR p: 0.798 Clarity of information G1: 6 G2: 6 95% CI, NR p: 0.296 Helpfulness of information G1: 6 G2: 5.8 95% CI, NR p: 0.624 Would want other decisions G1: 6.1 G2: 5.8 95% CI, NR p: 0.248 Would recommend to others G1: 6.4 G2: 6.2 95% CI, NR p: 0.435
Murray et al., 2007[36] NA	Improvement in patient satisfaction with pharmacy services from baseline to 12 months	Timeframe somewhat unclear; Baseline and 12 month values reported, so duration b/t measures 12 mos	Validated questionnaire	G1: NR G2: NR	G1: 1.0 G2: 0.7 95% CI, NR p: 0.022

Author, Year Trial Name	Patient satisfaction 1	Description of Timing of Measurement of Outcome	Data source	N	Results
Pearce et al., 2008[39] Cardiovascular Risk Education and Social Support (CaRESS) Trial	Rating of primary doctor	Twice over a 12-month period, at baseline and endpoint	Patient Healthcare Satisfaction Survey	**BL** G1 + G2: 98 G3: 86 **EP** G1 + G2: 71 G3: 67	**BL** G1 + G2: 9.3 G3: 9.2 95% CI, NR P (G1 + G2 vs. G3): 0.6931 (unadjusted), NA (adjusted) **EP** G1 + G2: 9.5 G3: 9.3 95% CI, NR P (G1 + G2 vs. G3): 0.0255 (unadjusted), 0.6372 (adjusted)
Powell et al., 1995[40] NA	Assessment of videotape intervention	Once in a randomly selected subset of G1 subjects during the study's 4th month	Mailed survey	G1: 84 G2: NA	**Very useful** (N (%)) G1: 41 (48.8%) G2: NA 95% CI, NR p: NR **Somewhat useful** (N (%)) G1: 33 (39.3%) G2: NA 95% CI, NR p: NR **Neutral** (N (%)) G1: 2 (2.4%) G2: NA 95% CI, NR p: NR **Not useful** (N (%)) G1: 8 (9.5%) G2: NA 95% CI, NR p: NR

Author, Year Trial Name	Patient satisfaction 1	Description of Timing of Measurement of Outcome	Data source	N	Results
Solomon et al., 1998[54] NA Gourley et al., 1998[55] NA	Hypertension group: Technical-Professional dimension- "Makes me feel secure about taking my medications" (item1)	One measurement at final visit	Pharma Care Questionnaire (PCQ)- Likert scale of 1 (strongly agree) to 5 (strongly disagree)	G1: 62 G2: 68	G1: 1.39 (0.49 SD) G2: 1.69 (0.68 SD) 95% CI, NR p: 0.004
Waalen et al., 2009[59] NA	Overall my treatment for osteoporosis has been a good experience	measured at 1 year and 30 days after study entry	self-report	G1: 68 G2: 58	**All/most of the time** N (%) G1: 58 (85.3) G2: 52 (89.7) **Some of the time** N (%) G1: 4 (5.9) G2: 0 (0) **A little / none of the time** N (%) G1: 6 (8.8) G2: 6 (10.3) Overall p: 0.17

Author, Year Trial Name	Patient satisfaction 1	Description of Timing of Measurement of Outcome	Data source	N	Results
Weymiller et al., 2007[62] Statin Choice Randomized Trial Jones et al., 2009[63] Statin Choice Randomized Trial	Acceptable amount of information	Once immediately after the intervention	Self-administered written questionnaire (7-point Likert scale question)	G1: 26 G2: 26 G3: 23 G4: 23 G1: 26 G2: 26 G3: 23 G4: 23	**N (%) responding 6 or 7 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 (6-7) G2: 7.0 (6-7) G3: 7.0 (5-7) G4: 7.0 (5-7) 95% CI, NR p: NR
Wilson et al., 2010[65] Better Outcomes of Asthma Treatment (BOAT)	Patient-Perceived Roles in Treatment Decision Making - patient vs. asthma care manager; only obtained for those in SDM and CDM but not UC	once following session 1; reported as mean rating of involvement on 5-point scale	survey - mailed in post cards	G1: 182 G2: 180	G1: 3.1 +/-.06 G2: 2.5 +/-.09 p: , 0.0001

Table D30. Patient satisfaction outcomes 2

Author, Year Trial Name	Patient satisfaction 2	Description of Timing of Measurement of Outcome	Data source	N	Results
Katon et al., 1995[24] NA	% of patients reporting antidepressant meds as helping somewhat to a great deal	baseline, 4 months	self-report	**Major depression group** N=91 **Minor depression group** N=126	**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[25] NA	% Rating antidepressant medication as helping somewhat to a great deal	4-month follow up	questionnaire		**Major Depression Group** G1: 80% G2: 58.3% p: <0.10 **Minor Depression Group** G1: 94.6% G2: 88.6% p: 0.36
Mann et al., 2010[34] The Statin Choice	Decisional Conflict Scale--support subscale, with lower scores representing less conflict	Immediately after intervention and control	self-report	G1: NR G2: NR	G1: 25.2 G2: 29.6 95% CI, NR p: 0.05
Pearce et al., 2008[39] Cardiovascular Risk Education and Social Support (CaRESS) Trial	Rating of overall health care	Twice over a 12-month period, at baseline and endpoint	Patient Healthcare Satisfaction Survey	**BL** G1 + G2: 98 G3: 86 **EP** G1 + G2: 71 G3: 67	**BL** G1 + G2: 9.3 G3: 9.2 95% CI, NR p (G1 + G2 vs. G3): 0.6931 (unadjusted), NA (adjusted) **EP** G1 + G2: 8.3 G3: 8.5 95% CI, NR p (G1 + G2 vs. G3): 0.0255 (unadjusted), 0.6709 (adjusted)

Author, Year Trial Name	Patient satisfaction 2	Description of Timing of Measurement of Outcome	Data source	N	Results
Powell et al., 1995[40] NA	Would like to receive more educational videotapes	Once in a randomly selected subset of G1 subjects during the study's 4th month	Mailed survey	G1: 97 G2: NA	**Yes (N (%))** G1: 66 (68.0%) G2: NA 95% CI, NR p: NR **No (N (%))** G1: 16 (16.5%) G2: NA 95% CI, NR p: NR **No response (N (%))** G1: 15 (15.5%) G2: NA 95% CI, NR p: NR
Solomon et al., 1998[54] NA Gourley et al., 1998[55] NA	Hypertension group: Knowledge dimension- "Helps me understand my illness" (item 2)	One measurement at final visit	Pharmaceutical Care Questionnaire (PCQ)- Likert scale of 1 (strongly agree) to 5 (strongly disagree)	G1: 62 G2: 68	G1:1.45 (0.59 SD) G2: 1.84 (0.77 SD) 95% CI, NR p: 0.002

Author, Year Trial Name	Patient satisfaction 2	Description of Timing of Measurement of Outcome	Data source	N	Results
Weymiller et al., 2007[62] Statin Choice Randomized Trial Jones et al., 2009[63] Statin Choice Randomized Trial	Acceptable clarity of information	Once immediately after the intervention	Self-administered written questionnaire (7-point Likert scale question)	G1: 26 G2: 26 G3: 23 G4: 23 G1: 26 G2: 26 G3: 23 G4: 23	**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 (5-7) G2: 6.5 (5-7) G3: 6.0 (4-7) G4: 6.0 (4-6) 95% CI, NR p: NR

Table D31. Patient satisfaction outcomes 3

Author, Year Trial Name	Patient satisfaction 3	Description of Timing of Measurement of Outcome	Data source	N	Results
Mann et al., 2010[34] The Statin Choice	Full decisional conflict scale	Measured immediately after intervention	Self-report	NR	G1: 25.5 G2: 28.5 95% CI, NR p: 0.1
Solomon et al., 1998[54] NA Gourley et al., 1998[55] NA	Answer to Pharmaceutical Care Questionnaire (PCQ) item 6 that intervention pharmacist: "Should give more complete explanation about my medications"; Likert scale of 1 (strongly agree) to 5 (strongly disagree)	Visit 5, at between 4 and 6 months	Self-report by patient	G1: 62 G2: 68	Mean (SD) G1 4.16 (0.93) G2 3.81 (1.03) 95% CI, NR p = 0.042
Weymiller et al., 2007[62] Statin Choice Randomized Trial Jones et al., 2009[63] Statin Choice Randomized Trial	Acceptable helpfulness of information	Once immediately after the intervention	Self-administered written questionnaire (7-point Likert scale question)	G1: 26 G2: 26 G3: 23 G4: 23 G1: 26 G2: 26 G3: 23 G4: 23	**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 (4-7) G2: 7.0 (5-7) G3: 5.0 (4-7) G4: 5.0 (4-7) 95% CI, NR p: NR

Table D32. Patient satisfaction outcomes 4

Author, Year Trial Name	Patient satisfaction 4	Description of Timing of Measurement of Outcome	Data source	N	Results
Weymiller et al., 2007[62] Statin Choice Randomized Trial Jones et al., 2009[63] Statin Choice Randomized Trial	Would recommend to others deciding on statins	Once immediately after the intervention	Self-administered written questionnaire (7-point Likert scale question)	G1: 26 G2: 26 G3: 23 G3: 23 G1: 26 G2: 26 G3: 23 G4: 23	**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 (4-7) G2: 7.0 (7-7) G3: 5.5 (4-7) G4: 6.0 (5-7) 95% CI, NR p: NR

Table D33. Patient satisfaction outcomes 5

Author, Year Trial Name	Patient satisfaction 5	Description of Timing of Measurement of Outcome	Data source	N	Results
Weymiller et al., 2007[62] Statin Choice Randomized Trial Jones et al., 2009[63] Statin Choice Randomized Trial	Would prefer similar approach for other treatment choices	Once immediately after the intervention	Self-administered written questionnaire (7-point Likert scale question)	G1: 26 G2: 26 G3: 23 G4: 23 G1: 26 G2: 26 G3: 23 G4: 23	**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 to 3.8 p: NR **Mean (95% CI)** G1: 6.0 (4-7) G2: 7.0 (5-7) G3: 6.0 (4-7) G4: 6.0 (4-7) 95% CI, NR p: NR

Table D34. Patient satisfaction outcomes 6

Author, Year Trial Name	Patient satisfaction 6	Description of Timing of Measurement of Outcome	Data source	N	Results
Weymiller et al., 2007[62] Statin Choice Randomized Trial Jones et al., 2009[63] Statin Choice Randomized Trial	Overall acceptability	Once immediately after the intervention	Self-administered written questionnaire (7-point Likert scale question)	G1: 26 G2: 26 G3: 23 G3: 23 G1: 26 G2: 26 G3: 23 G4: 23	**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 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

Table D35. Quality of life outcomes 1

Author, Year Trial Name	Quality of life 1	Description of Timing of Measurement of Outcome	Data source	N	Results
Bender et al., 2010[1] NA	Asthma quality of life questionnaire - Total; higher scores indicate better quality of life	measured at baseline and at week 10; time frame of measure NR	Asthma quality of life questionnaire (AQLQ)	G1: 25 G2: 25	**Mean change in AQLQ scores** G1: 0.152 (0.92) G2: 0.381 (1.06) 95% CI, p: .419
Janson et al., 2009[21] NA	Mean change in Quality of life score (range0-80; lower scores mean higher quality):During intervention(T0-T1), following intervention (T1-T2), and for entire study duration (T0-T2)	frequency not reported; assume once at the end of each time period;	validated self-competed questionnaire	G1: 45 G2: 39	**T0-T1** G1: -2.71 G2: -1.39 p: 0.36 **T1-T2** G1: -1.11 G2: 0.58 95% CI, p: .27 **T0-T2**: G1: -3.82 G2: -0.80 p: 0.06
Janson et al., 2003[20] NA	Quality of life at week 7; between group difference in change from baseline to final visit at week 7 (95% CI)	assessed at baseline and week 7; time frame not reported	questionnaire	G1: 33 G2: 32	G1: 17 (9) G2: 19 (13) Between group difference: -4.4 (-9 to 0.2) , p=0.06
Murray et al., 2007[36] NA	Improved Disease-specific QOL from baseline to 6 months	Timeframe unclear; measured at baseline and 6 months; 6 mos b/t measures	CHF questionnaire	G1: NR G2: NR	G1: 0.28 G2: 0.21 95% CI, NR p: 0.52
Wilson et al., 2010[65] Better Outcomes of Asthma Treatment (BOAT)	Asthma-related quality of life survey results - consists of five-item Symptom Subscale of theJuniper Mini Asthma Quality of Life Questionnaire	administered at baseline and end of follow-up year 1; questions refer to previous 2 weeks ; data reported as mean symptom subscale scores	self-report	G1: 182 G2: 180 G3: 189	G1: 5.5 G3: 5.1; p= 0.0003 G1: 5.5 G2: 5.4 p: >.05 G2: 5.4 G3: 5.1 p: .0009

Table D36. Quality of life outcomes 2

Author, Year Trial Name	Quality of life 2	Description of Timing of Measurement of Outcome	Data source	N	Results
Murray et al., 2007[36] NA	Improved Disease-specific QOL from baseline to 12 months	Timeframe unclear; measured at baseline and 6 months; 6 mos b/t measures	CHF questionnaire	G1: NR G2: NR	G1: 0.39 G2: 0.24 95% CI, NR p: 0.21

Table D37. Health utilization outcomes 1

Author, Year Trial Name	Health utilization 1	Description of Timing of Measurement of Outcome	Data source	N	Results
Janson et al., 2009[21] NA	Beta-agonist use, During intervention(T0-T1), following intervention (T1-T2), and for entire study duration (T0-T2)	collected once at the end of each time period, reported as incidence rate ratios	NR	G1: 45 G2: 39	**T0-T1**: G1: 0.6 G2: 0.8 p: 0.01 **T1-T2**: G1: 0.5 G2: 0.5 p: 0.98 **T0-T2**: G1: 0.3 G2: 0.4 p: 0.3
Katon et al., 1996[25] NA	Visits with primary care physician	6-month period after the primary care referral visit	medical records	NR	Mean (SD) G1: 4.6 (2.6) G2: 4.1 (2) p: 0.19
Katon et al., 1999[26] NA Katon et al., 2002[27] NA	Mean number of visits with primary care providers (Reported in 9123)	Measured at 12 weeks & 6 months	Not indicated; likely to be documented study managers or psychiatrist	NR	**Mean (SD) at 12 weeks** G1: 1.6 (1.8) G2: 1.8 (1.8) Chi-square: 1.46 p: 0.23 **At 6 mos** G1: 3.4 (4.3) G2: 3.3 (3.1) Chi-square: 0.35 p: 0.55
Katon et al., 1995[24] NA	Primary care physician visits for depression (non-study visits) Intervention patients: Number of study visits for collaborative care intervention	1-year period beginning with the primary care referral visit	HMO medical records	G1: 108 G2: 109	Mean number of visits (SD): G1: 4.5 (3.7) G2: 3.7 (2.4) Intervention: (N=G1=108) Mean # study visits (SD) 3.9 (2.5)

Author, Year Trial Name	Health utilization 1	Description of Timing of Measurement of Outcome	Data source	N	Results
Katon et al., 1996[25] NA	Seen by mental health specialist	First 12 weeks after the primary care referral visit6-month period after primary care referral visit	medical records	NR	**% seen by mental health specialist (first 12 weeks)** G1: 20% G2: 29% p: 0.21 **% seen by mental health specialist (first 6 months)** G1: 24% G2: 33% p: 0.21
Murray et al. (continued), 2007[36] NA	All-cause Hospitalizations	Timeframe: 30 days. Assessed via monthly telephone interviews x 12	Ascertained through monthly interviews, confirmed (?) by medical record review by an RN	G1: 122 G2: 192	Mean (SD) G1: 0.78 (1.66), 0 median G2: 0.97 (1.78), 0 median IRR 0.81 (95% CI, 0.64 to 1.04) p: NR
Murray et al., 2007[36] NA	Combined all-cause ED visits and Hospitalizations	Timeframe: 30 days. Assessed via monthly telephone interviews x 12	Ascertained through monthly interview, confirmed by medical record review by an RN	G1: 122G2: 192	Mean (SD) G1: 2.94 (4.69), 1 median G2: 3.65 (6.26), 1.5 median IRR 0.82 (95% CI 0.72 to 0.93) p: NR
Rich et al., 1996[42] NA	Number of patients having readmissions	Measured during 90 days following discharge	NR	G1: 80 G2: 76	G1: 18 (22.5%) G2: 22 (28.9%) 95% CI, NR p: NS.
Ross et al., 2004[44] NR	Number of patients with hospitalizations (%); Number of hospitalizations	NR	chart review	G1: NR G2: NR	**Number of pts** (%) G1: 11 (20%) G2: 12 (23%) 95% CI, NR p: 0.81; **Number of hospitalizations** G1: 22 G2: 21 95% CI, NR p: 1.00

Author, Year Trial Name	Health utilization 1	Description of Timing of Measurement of Outcome	Data source	N	Results
Rudd et al., 2004[45] NA	Number of medication changes over 6 months in each group	NR	NR	NR	G1: 223 (6 SD) G2: 52 (1 SD) 95% CI, NR p: <0.01
Schneider et al., 2008[49] NA	Emergency department visits and hospitalizations	6 and 12 months for the past 6 months	Medical chart review	G1: 47 G2: 38	G1: NR G2: NR 95% CI, NR p: NR Numbers not reported, but results were NS
Solomon et al., 1998[54] NA Gourley et al., 1998[55] NA	Hypertension group: Emergency room visits in 4 weeks prior, compared between groups	Visit 5, at between 4 and 6 months	Self-report by patient	G1: 63 G2: 61	G1: 0.05 (0.22 SD) G2: 0.13 (0.39 SD) 95% CI, NR p: NR
Weymiller et al., 2007[62] Statin Choice Randomized Trial Jones et al., 2009[63] Statin Choice Randomized Trial	Statin therapy start among those not already receiving it	Twice, immediately after clinician visits & during 3 month follow-up	Self-report	G1: 23 G2: 19	**BL (N (%))** G1: 7 (30%) G2: 4 (21%) 95% CI, NR p: NR **Follow-up (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

Author, Year Trial Name	Health utilization 1	Description of Timing of Measurement of Outcome	Data source	N	Results
Wilson et al., 2010[65] Better Outcomes of Asthma Treatment (BOAT); note that there is online supplemental material for methods and timeline	average asthma related visits per year	measured once at end of year 1, includes entire year	electronic records from KP	G1: 204 G2: 204 G3: 204	G1: 1.0/yr G3: 1.4/yr Group differences:-0.36 95% CI, -0.66 to -0.07 p= 0.0161 G1:1.0/yr G2:1.1/yr Group differences: 0.01 95% CI, -0.29t o 0.30 p: =.97 G2: 1.1/yr G3: 1.4/yr Group differences: -0.37 95% CI, -0.67 to -0.07 p: 0.0147

Table D38. Health utilization outcomes 2

Author, Year Trial Name	Health utilization 2	Description of Timing of Measurement of Outcome	Data source	N	Results
Katon et al., 1999[26] NA Katon et al., 2002[27] NA	Percentage seen at least once by a non-study mental health specialist in group-model HMO (Reported in 9123)	Measured at 12-weeks & 6 months	Not indicated; likely to be self-report	NR	**At 12-wks**: G1: 17.5% G2: 24.6% Chi-square: 1.29 p: 0.26 **At 6-mos** G1: 24.6% G2:27.2% Chi-square: 0.09 p: 0.76
Katon et al., 1995[24] NA	Seen by a mental health specialist Seen by a psychiatrist	NA	HMO medical records	G1: 108 G2: 109	**Number (%)** seen by mental health specialist: G1: 30 (27%) G2: 34 (31%) **Number (%)** seen by Psychiatrist: G1: 3 (3%) G2: 11 (10%)
Katon et al., 1996[25] NA	Visits with primary care physician	first 12 weeks of treatment	medical records	NR	mean (SD) G1: 3.1 (1.7) G2: 2.9 (1.4) p: 0.30
Murray et al. (continued), 2007[36] NA	Cardiovascular-related combined ED visits and hospitalizations	Timeframe: 30 days. Assessed via monthly telephone interviews x 12	Ascertained through monthly interviews, confirmed (?) by medical record review by an RN	G1: 122 G2: 192	Mean (SD) G1: 0.61 (1.72) G2: 0.67 (1.95) IRR 0.96 (95% CI, 0.48 to 1.91) p: NR
Murray et al., 2007[36] NA	All-cause Emergency Department Visits	Timeframe: 30 days. Assessed via monthly telephone interviews x 12	Ascertained through monthly interviews, confirmed (?) by medical record review by an RN	G1: 122 G2: 192	Mean (SD) G1: 2.16 (3.31), 1 median G2: 2.68 (4.87), 1 median IRR 0.82 (95% CI, 0.70 to 0.95) p: NR

Author, Year Trial Name	Health utilization 2	Description of Timing of Measurement of Outcome	Data source	N	Results
Rich et al., 1996[42] NA	Number of readmissions	Measured during 90 days following discharge	NR	G1: 80 G2: 76	G1: 22 G2: 31 95% CI, NR p: NS
Ross et al., 2004[44] NR	Number of patients with ER visits (%); Number of ER visits	NR	chart review	G1: NR G2: NR	**Number of pts (%)**: G1: 11 (20%) G2: 7 (13%) 95% CI, NR p: 0.44; **Number of visits**: G1: 20 G2: 8 95% CI, NR p: 0.03** more in interventions grp
Solomon et al., 1998[54] NA Gourley et al., 1998[55] NA	Hypertension group: hospitalizations in 4 weeks prior, compared between groups	Visit 5, at between 4 and 6 months	Self-report by patient	G1: 63 G2: 61	G1: 0.02 (0.13 SD) G2: 0.10 (0.35 SD) 95% CI, NR p: <0.05 (one-tailed)
Weymiller et al., 2007[62] Statin Choice Randomized Trial Jones et al., 2009[63] Statin Choice Randomized Trial	Total statin therapy usage at follow-up	Once, at 3 month follow-up	Self-report	G1: 52 G2: 46	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

Author, Year Trial Name	Health utilization 2	Description of Timing of Measurement of Outcome	Data source	N	Results
Wilson et al., 2010[65] Better Outcomes of Asthma Treatment (BOAT)	SABA use; data reported as mean equivalents acquired	year 1	electronic pharmacy data	G1: 182 G2: 180 G3: 189	G1: 6.5 G3:8.1 p= 0.002 G1: 6.5 G2: 7.1 p: 0.09 G2: 7.1 G3:8.1 p: 0.038

Table D39. Health utilization outcomes 3

Author, Year Trial Name	Health Utilization 3	Description of Timing of Measurement of Outcome	Data Source	N	Results
Katon et al., 1999[26] NA Katon et al., 2002[27] NA	Mean number of visits to a non-study mental health specialist in group-model HMO (Reported in 9123)	Measured at 12-weeks & 6 months	Not indicated; likely to be self-report	NR	**At 12-wks:** G1: 0.6 (1.7) G2: 0.8 (1.9) p: 0.34 **At 6-mos**. G1: 1.3 (2.9) G2: 1.3 (2.9) p: 0.85
Katon et al., 1996[25] NA	Visits with primary care physician	6-month period after the primary care referral visit	Medical records	NR	Mean (SD) G1: 4.6 (2.6) G2: 4.1 (2) p: 0.19
Murray et al., 2007[36] NA	Heart failure-related combined ED visits and hospitalizations	Timeframe: 30 days. Assessed via monthly telephone interviews x 12	Ascertained through monthly interviews, confirmed (?) by medical record review by an RN	G1: 122 G2: 192	G1: 0.40 mean (1.47 SD) G2: 0.44 mean (1.79 SD) IRR 1.00 (95% CI 0.36 to 2.77) p: NR
Rich et al., 1996[42] NA	Days of hospitalization from readmissions	Measured during 90 days following discharge	NR	G1: 80 G2: 76	G1: 188 G2: 258 95% CI, NR p: NS, no # given
Ross et al., 2004[44] NR	Number of patients with heart failure practice visits (%); Number of heart failure practice visits	NR	Chart review	G1: NR G2: NR	Number of pts: G1: 50 (93%) G2: 49 (92%) 95% CI, NR p: 1.00; Number of visits: G1: 324 G2: 325 95% CI, NR p: 0.66
Solomon et al., 1998[54] NA Gourley et al., 1998[55] NA	Hypertension group: contacts with "other healthcare providers" (MD, NP, PA or RN) in 4 weeks prior, compared between groups	Visit 5, at between 4 and 6 months	Self-report by patient	G1: 63 G2: 61	G1: 0.59 (0.78 SD) G2: 1.0 (0.82 SD) 95% CI, NR p: <0.05 (one-tailed)

Author, Year Trial Name	Health Utilization 3	Description of Timing of Measurement of Outcome	Data Source	N	Results
Wilson et al., 2010[65] Better Outcomes of Asthma Treatment (BOAT)	SABA use; data reported as mean equivalents acquired	Year 2	Electronic pharm data	G1: 182 G2: 180 G3: 189	G1: 4.7 G3: 6.3 p= 0.0141 G1: 4.7 G2: 6.0 p: 0.06 G2: 6.0 G3:6.3 p: >0.05

Table D40. Costs outcomes 1

Author, Year Trial Name	Costs 1	Description of Timing of Measurement of Outcome	Data source	N	Results
Choudhry et al., 2011[13]	Health care spending by patients and insurers	Using the allowed amounts appearing in the insurers' claims data for prescription medications, nondrug medical services (i.e., physician visits, emergency room admissions, hospitalizations, and outpatient procedures), and the combination of these two factors after the assignment of the patient to a study group	Health claims database	G1: 2845 G2: 3010	**Insurer** G1: $64,726 (639,683) G2: $69,997 (617,650) Relative spending: 0.92 (0.55 to 1.56) p: 0.77 **Patient**: G1: $1,282 (1549) G2: $1,781 (2,263) Relative spending: 0.74 (0.68 to 0.80) p<0.001 **Combined** G1:$66,008 (639,970) G2: $71,778 (618,055) Relative spending: 0.89 (0.50 to 1.56) p=0.68
Katon et al., 1999[26] NA Katon et al., 2002[27] NA	Depression treatment costs; and non-depression-related outpatient costs (Reported in 3169)	36 months; 6 months prior to randomization and 30 months after randomization	Health plan computerized data	G1: 95 G2: 92	**Depression** Unclear whether costs refer to outpatient only or total costs. F(1,173): 2.65 p: 0.10 (Due to the increased costs of longer-term use of SSRIs) **Non-depression outpatient costs** mean (95% CI) G1: $6769 (5351 to 8188) G2: $5470 (4431 to 6510) F(1,180): 0.11 p: 0.74
Murray et al., 2007[36] NA	Total costs (inpatient and outpatient)	NR	Fixed costs for training, variable costs based on observed time spent	G1: 122 G2: 192	G1: $ 11034 mean (17211 SD) G2: $ 14199 (23672) Difference: -3165 (95% CI, -7800 to 1138) p: NR
Murray et al., 2007[36] NA	Inpatient healthcare costs	NR	Fixed costs for training, variable costs based on observed time spent	G1: 122 G2: 192	G1: $ 5550 mean (13847 SD) G2: $ 7827 (20413) Difference: -2277 (95% CI, -6329 to 1225) p: NR

Table D41. Costs outcomes 2

Author, Year Trial Name	Costs 2	Description of Timing of Measurement of Outcome	Data source	N	Results
Katon et al., 1999[26] NA Katon et al., 2002[27] NA	Total ambulatory costs; and Total Health care costs (Reported in Katon et al., 1999)	36 months; 6 months prior to randomization and 30 months after randomization	Health plan computerized data	G1: 95 G2: 92	**Amb. costs** mean (95% CI) G1: $8524 (5059 to 8188) G2: $7787 (6595 to 8980) F(1,180): 0.77 p: 0.40 **Total healthcare costs** mean (95% CI): G1: $9799 (7763 to 11834) G2: 9192 (7504 to 10880) F(1,180)=0.91 p= 0.34
Murray et al., 2007[36] NA	Outpatient healthcare costs	Unclear	Fixed costs for training, variable costs based on observed time spent	G1: 122 G2: 192	G1: $ 5483 mean (6434 SD) G2: $6373 (6501) Difference: -886 (95% CI, -2289 to 660) p: NR

Table D42. Adverse event outcomes 1

Author, Year Trial Name	Adverse Events 1	Description of Timing of Measurement of Outcome	Data Source	N	Results	Did the intervention(s) result in worsened health or other outcomes? If so, list worsened outcomes here
Carter et al., 2009[10] NA	Mean total adverse effect score	Measured twice, once at baseline & once at 6 month follow-up	Adverse event questionnaire with 47 items, developed for another study & personally administered by study nurses	G1: 192 G2: 210	**BL** (Mean (SD)) G1: 28.0 (23.0) G2: 42.1 (24.2) 95% CI, NR p: <0.001 **6 month follow-up** (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.	No
Murray et al., 2007[36] NA	Number of patients who had an adverse drug event or medication error	NR	Measured using a program that identified adverse events from the medical record system	G1: 112 (unclear why different from 122 for every other outcome) G2: 192	G1: 42 (37.5%) G2: 91 (47.4%) 95% CI, NR p: Chi-sq 0.094; between-group rate comparison 0.108	No
Schectman et al., 1994[48] NA	Proportion of patients reporting of adverse events associated with medications at 2 months	2 months; measured at 2, 4, and 6 months though only 2 month results reported	Self-report to clinic staff	Niacin: G1: 40 G2: 40 BAS: G1: 18 G2: 20	Niacin: flushing, pruritus, 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	No

Author, Year Trial Name	Adverse Events 1	Description of Timing of Measurement of Outcome	Data Source	N	Results	Did the intervention(s) result in worsened health or other outcomes? If so, list worsened outcomes here
Weymiller et al., 2007[62] Statin Choice Randomized Trial Jones et al., 2009[63] Statin Choice Randomized Trial	Termination of statin use due to associated adverse events	NR	Clinician assessment	G1: 52 G2: 46	G1: 0 G2: 2 95% CI, NR p: NR	No

Table D43. Other subgroup outcomes 1

Author, Year Trial Name	Subgroup	Outcome 1 for subgroup	Description of Timing of Measurement of Outcome	Data source	N	Results
Bogner et al., 2008[4] NA	Depression and hypertension	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction
Bogner et al., 2010[5] NA	African American primary care patients (entire sample)	Depressive symptoms	2 times, once at baseline and once at 12 weeks	Center for Epidemiologic Studies Depression Scale (CES-D)	G1: 29 G2: 29	**BL** G1: Mean (SD) = 15.6 (11.7) G2: Mean (SD) = 19.7 (16.7) 95% CI, NR p: 0.47 **EP** G1: Mean (SD) = 9.6 (9.4) G2: Mean (SD) = 16.6 (14.5) 95% CI, NR p: 0.035
Fulmer et al., 1999[15] NA	Elderly	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction
Katon et al., 1995[24] NA	Major depression	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction
Katon et al., 1996[25] NA	Major depression	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction
Katon et al., 1999[26] NA Katon et al., 2002[27] NA	Moderate severity of depression (Reported in 3169)	Depression severity and functional impairment in patients with moderate-severity depression at baseline	Measured at 1, 3, 6, and 28 months; analysis at 28 months	SCL Depression scale (for depression severity); Sheehan disability score (for functional impairment)	G1: NR G2: NR	Depression severity: ANCOVA: F(1,187) = 8.65 Adjusted mean, (SD): G1: 0.88, (0.52) G2: 1.23, (0.62) p: 0.004 Sheehan Disability Score ANCOVA: F(1.87) = 1.21 Adjusted mean, (SD): G1: 3.09, (2.30) G2: 3.58, (2.37) p: 0.27

Author, Year Trial Name	Subgroup	Outcome 1 for subgroup	Description of Timing of Measurement of Outcome	Data source	N	Results
Lee et al. (continued), 2006[31] FAME	Patients with drug-treated hypertension	Drug treated hypertension patients only: Difference in Diastolic BP at 14 months (95% CI)	Difference between SBP values at 14 months and at 2 months; frequency = 2 measurements; duration between measures = 12 months	Clinical pharmacist measurement	G1: 73 G2: 62	G1: -2.5 (-4.9 to -0.2) G2: -1.2 (-3.7 to 1.2) 95% CI, NR p: 0.39
Lee et al., 2006[31] FAME	Patients with drug-treated hypertension	Drug treated hypertension patients only: Systolic BP at 14 months, mean (SD)	At 14 months; 1 time measure for this outcome (avg of 2nd and 3rd BP measurements from that visit)	Clinical pharmacist measurement	G1: 73 G2: 62	G1: 124.4 (14.0) G2: 133.3 (21.5) 95% CI, NR p: 0.005
Lin et al., 2006[32] NA	Depression and diabetes	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction
Rich et al., 1996[42] NA	Elderly (≥70 years of age)	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction
Schneider et al., 2008[49] NA	Elderly, i.e., ≥65 years of age (entire sample)	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction

Table D44. Other subgroup outcome 2

Author, Year Trial Name	Subgroup	Outcome 2 for Subgroup	Description of Timing of Measurement of Outcome	Data source	N	Results
Bogner et al., 2008[4] NA	Depression and hypertension	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction
Bogner et al., 2010[5] NA	African American primary care patients	A1C/Blood glycemic control	2 times, at baseline and 12 weeks	A1C assays	G1: 29 G2: 29	**BL (%)** G1: Mean (SD) = 7.3 (2.3) G2: Mean (SD) = 7.3 (2.0) 95% CI, NR p: 0.70 **EP (%)** G1: Mean (SD) = 6.7 (2.3) G2: Mean (SD) = 7.9 (2.6) 95% CI, NR p: 0.019
Fulmer et al., 1999[15] NA	Elderly	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction
Katon et al., 1995[24] NA	Major depression	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction
Katon et al., 1996[25] NA	Major depression	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction
Katon et al., 1999[26] NA Katon et al., 2002[27] NA	Severe depression at baseline (Reported in 3169)	Depression severity and functional impairment in patients with Severe depression at baseline	Measured at 1, 3, 6, and 28 months; analysis at 28 months	SCL Depression scale (for depression severity); Sheehan disability score (for functional impairment)	G1: NR G2: NR	Depression severity: ANCOVA: F(1.51)=0.02 Adjusted mean, (SD): G1: 1.16, (0.85) G2: 1.19, (0.72) p: 0.88 Sheehan disability score: ANCOVA: F(1.51) = 0.09 Adjusted mean, (SD): G1: 3.41, (2.61) G2: 3.20, (2.66) p: 0.76

Author, Year Trial Name	Subgroup	Outcome 2 for Subgroup	Description of Timing of Measurement of Outcome	Data source	N	Results
Lee et al. (continued), 2006[31] FAME	Patients with drug-treated hyperlipidemia	Drug-treated hyperlipidemia patients only: LDL-C at 14 months, mean (SD)	At 14 months; 1 time measure for this outcome	Direct assay measurement	G1: 64 G2: 57	G1: 87.5 (24.2) G2: 88.4 (21.0) 95% CI, NR p: 0.84
Lee et al., 2006[31] FAME	Patients with drug-treated hypertension	Drug treated hypertension patients only: Difference in Systolic BP at 14 months (95% CI)	Difference between SBP values at 14 months and at 2 months; frequency = 2 measurements; duration between measures = 12 months	Clinical pharmacist measurement	G1: 73 G2: 62	G1: -6.9 (-10.7 to -3.1) G2: -1.0 (-5.9 to 3.9) 95% CI,NR p: 0.04
Lin et al., 2006[32] NA	Depression and diabetes	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction
Rich et al., 1996[42] NA	Elderly (≥70 years of age)	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction
Schneider et al., 2008[49] NA	Elderly, i.e., ≥65 years of age (entire sample)	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction	See main outcomes abstraction

Table D45. Other subgroup outcome 3

Author, Year Trial Name	Subgroup	Outcome 3 for Subgroup	Description of Timing of Measurement of Outcome	Data Source	N	Results
Lee et al., 2006[31] FAME	Patients with drug-treated hypertension	Drug treated hypertension patients only: Diastolic BP at 14 months, mean (SD)	At 14 months; 1 time measure for this outcome (avg of 2nd and 3rd BP measurements from that visit)	Clinical pharmacist measurement	G1: 73 G2: 62	G1: 67.5 (9.9) G2: 68.6 (10.5) 95% CI, NR p: 0.54
Lee et al. (continued), 2006[31] FAME	Patients with drug-treated hyperlipidemia	Drug-treated hyperlipidemia patients only: Difference in LDL-C at 14 months, mean (95% CI)	Difference between SBP values at 14 months and at 2 months; frequency = 2 measurements; duration between measures = 12 months	Direct assay measurement	G1: 64 G2: 57	G1: -2.8 (-8.1 to 2.5) G2: -5.8 (-11.0 to -0.6) 95% CI, NR p: 0.85
Solomon et al., 1998[54] NA Gourley et al., 1998[55] NA	Hypertension arm only	Systolic BP at T1 comparing Visit 5 intervention and control groups	Baseline	Vital signs measured by pharmacist	G1: 63 G2: 70	G1: 138.5 (13.9) G2: 144.9 (21.3) 95% CI, NR p: 0.044

Table D46. Applicability

Author, Year Trial Name	Is the study population broadly applicable? Comments if "no" response	Is the intervention broadly applicable? Comments if "no" response	Is the comparator broadly applicable? Comments if "no" response	Are the outcomes broadly applicable? Comments if "no" response
Bender et al., 2010[1] NA	Unclear or NR Small study population and vague exclusion criteria; difficult to assess applicability	Yes	Yes	Yes
Berg et al., 1997[2] NA	No Mostly white and insured	Yes	Yes	Yes
Berger et al., 2005[3] NA	No Recruitment was stratified by stage of readiness to change, which likely makes the population not representative	Yes	No No attention-matched control program	Unclear or NR Insufficient information given about persistence measure
Bogner et al., 2008[4] NA	Yes	Yes	Yes	Yes
Bogner et al., 2010[5] NA	Yes	Yes	Yes	Yes
Bosworth et al., 2008[7] TCYB Bosworth et al., 2007[8] TCYB Methods paper	No Population limited to 8 county area; certain co-morbidities excluded (i.e., MI, revascularization, stroke, etc.)	Yes	Yes	Yes
Bosworth et al., 2005[6] V-STITCH	No Only veterans at Durham VA hospital	Yes	Yes	Yes
Capoccia et al., 2004[9] NA	No Study population consisted primarily of white women	Yes	Yes	Yes
Carter et al., 2009[10] NA	Yes	Yes	Yes	Yes

Author, Year Trial Name	Is the study population broadly applicable? Comments if "no" response	Is the intervention broadly applicable? Comments if "no" response	Is the comparator broadly applicable? Comments if "no" response	Are the outcomes broadly applicable? Comments if "no" response
Chernew et al., 2008[11] NA	Yes	Yes	Yes	Yes
Choudhry et al., 2010[12] NA	Yes	Yes	Yes	Yes
Choudhry et al., 2011[13] MI FREEE	Yes	Yes	Yes	Yes
Friedman et al., 1996[14] NA	Yes	Yes	Yes	Yes
Fulmer et al., 1999[15] NA	No Only 10% participation rate	No Phone intervention would be applicable, but videophone technology is not widely available	Yes	Yes
Grant et al., 2003[16] NA	No One clinic with little ethnic diversity makes this different than overall populations of patients with type 2 diabetes mellitus; Is based in community clinic rather than tertiary care but is academic-affiliated and thus less generalizable	Yes	Yes	Yes
Guthrie et al., 2001[17] First Myocardial Infarction (MI) Risk Reduction Program	No Limited to participants in a registry program who received 2-week supply of pravastatin free	Yes	Yes	No Short term measure of medication adherence with unvalidated measure
Hoffman et al., 2003[18] NA	Yes	Yes	Yes	Yes

Author, Year Trial Name	Is the study population broadly applicable? Comments if "no" response	Is the intervention broadly applicable? Comments if "no" response	Is the comparator broadly applicable? Comments if "no" response	Are the outcomes broadly applicable? Comments if "no" response
Hunt et al., 2008[19] NA	Yes	Yes	Yes	Yes
Janson et al., 2003[20] NA	Yes	Yes	Yes	No The study was only 7 weeks in duration - follow-up may be too short
Janson et al., 2009[21] NA	No Relatively high levels of education and employment	Yes	Yes	Yes
Johnson et al., 2006[23] NR	Yes	Yes	Yes	No Non-adherence measure contains 5 items: taken less of medication than doctor recommended; taken a break from medication; forgot a dose; taken a dose late or not at all; stopped taking medication because you felt better)
Johnson et al., 2006[22] NR	Yes	Yes	Yes	No Non-adherence measure contains 5 items: taken less of medication than doctor recommended; taken a break from medication; forgot a dose; taken a dose late or not at all; stopped taking medication because you felt better)
Katon et al., 1995[24] NA	Yes	Yes	No No attention-control condition	Yes
Katon et al., 1999[26] NA Katon et al., 2002[27] NA	Yes	Yes	Yes	Yes

Author, Year Trial Name	Is the study population broadly applicable? Comments if "no" response	Is the intervention broadly applicable? Comments if "no" response	Is the comparator broadly applicable? Comments if "no" response	Are the outcomes broadly applicable? Comments if "no" response
Katon et al., 2001[28] NA Ludman et al., 2003[29] NA Van Korff et al., 2003[30] NA	Yes	Yes	Yes	Yes
Katon et al., 1996[25] NA	No Mostly white and middle class	Yes	Yes	Yes
Lee et al., 2006[31] FAME	Yes	Yes	Yes	No
Lin et al., 2006[32] NA	No Narrow eligibility criteria and exclusions for those with comorbidities	Unclear or NR Unsure whether training that intervention nurses received in depression diagnosis, pharmacotherapy, behavioral activation, and problem-solving treatment could be broadly applied	Yes	Yes
Maciejewski et al., 2010[33] NA	Yes	Yes	Yes	Yes
Mann et al., 2010[34] The Statin Choice	No Conducted at one urban minority practice with mostly African American and Latino participants. Thus while good to apply to these patients, may not apply broadly to all patients with diabetes.	Yes	Yes	Yes

Author, Year Trial Name	Is the study population broadly applicable? Comments if "no" response	Is the intervention broadly applicable? Comments if "no" response	Is the comparator broadly applicable? Comments if "no" response	Are the outcomes broadly applicable? Comments if "no" response
Montori et al., 2011[35] NA	Yes	Yes	Yes	Yes
Murray et al., 2007[36] NA	Yes	No All participants obtained meds at one pharmacy with a pharmacist trained in multiple disciplines who took time to assess for adherence, etc. and intervened as needed	Yes	Yes
Nietert et al., 2009[37] NA	Yes	Unclear or NR The level of follow-up that pharmacists conducted in this study for the interventions was greater than the care they usually provided.	Yes	Yes
Okeke et al., 2009[38] NA	Yes	No Dosing aids are not used in typical practice; however, it seems that they could be easily incorporated.	No There was no attention-matched control condition.	Yes
Pearce et al., 2008[39] Cardiovascular Risk Education and Social Support (CaRESS) Trial	Yes	Yes	Yes	Unclear or NR The medication adherence measure used in this study was not clearly described by the investigators, so it is unclear whether it is "broadly applicable". The answer may be "No" to the quality of life measures, which were composite measures from the SF-36 Health Survey.
Powell et al., 1995[40] NA	Yes	Yes	Yes	Yes

Author, Year Trial Name	Is the study population broadly applicable? Comments if "no" response	Is the intervention broadly applicable? Comments if "no" response	Is the comparator broadly applicable? Comments if "no" response	Are the outcomes broadly applicable? Comments if "no" response
Powers et al., 2011[68]	No	No	Yes	No
NA	only VA population so not broadly applicable	intervention is very individualized so may difficult to implement in real practice		self-reported med adherence only measured at 3 months
Pyne et al., 2011[41]	No	Yes	Yes	Yes
HIV Translating Initiatives for Depression Into Effective Solutions (HITIDES)	Almost exclusively men in study pop			
Rich et al., 1996[42]	No	No	No	No
NA	Unclear exclusion criteria - "other severe illness??", age >70	Very complex intervention with multiple disciplines, broadly defined intensity of intervention from inpt and outpt standpoint	Comparator was not well-defined - were people getting any home visits, etc.?	Outcomes had 2 different methods of calculation (individual vs. all meds); also proportions of people taking >80% of meds; only one short-term measure of adherence
Rickles et al., 2005[43]	No	Yes	Yes	Yes
NA	vast majority of participants were white women, patients could not have comorbid illness requiring medication			
Ross et al., 2004[44]	No	Yes	Yes	Yes
NR	Substantial differences between participants who responded to survey and non-responders; non-responders with less education, fewer white non-Hispanic, more with low income, more with safety-net insurance, less computer access			

Author, Year Trial Name	Is the study population broadly applicable? Comments if "no" response	Is the intervention broadly applicable? Comments if "no" response	Is the comparator broadly applicable? Comments if "no" response	Are the outcomes broadly applicable? Comments if "no" response
Rudd et al., 2004[45] NA	Yes	Yes	Yes	Unclear or NR Yes for MEMS, No for clinical outcome since BP is only a surrogate measure
Rudd et al., 2009[46] NA	Yes	Yes	No There was no attention-matched control condition	No Very little information is provided about the self-report adherence measure used in the study.
Schaffer et al., 2004[47] NA	Unclear or NR Eligibility criteria not reported	Yes	Yes	Yes
Schectman et al., 1994[48] NA	Yes	Yes	Yes	Yes
Schneider et al., 2008[49] NA	Yes	Yes	Yes	Yes
Schnipper et al., 2006[50] NA	Yes	Yes	No No attention-matched control program	Yes
Simon et al., 2006[51] NA	Yes	Yes	Yes	Yes
Sledge et al., 2006[52] NA	No Patients with higher health care costs were over-sampled, and so the intervention was conducted among a group with very high inpatient health service use. This plus the exclusion of outliers and those with high morbidity creates a sample that is not broadly applicable.	No Intensity may not be feasible for routine use	No No attention-matched control program	Unclear or NR
Smith et al., 2008[53] NR	Yes	Yes	Yes	Yes

Author, Year Trial Name	Is the study population broadly applicable? Comments if "no" response	Is the intervention broadly applicable? Comments if "no" response	Is the comparator broadly applicable? Comments if "no" response	Are the outcomes broadly applicable? Comments if "no" response
Solomon et al., 1998[54] NA Gourley et al., 1998[55] NA	No Very few patients with HTN are on only a dihydropyridine or a dihydropyridine & a diuretic.	Unclear or NR The actual content of the intervention was unclear and was delivered by pharmacy residents - limits the applicability of the intervention as the number of pharmacy residencies is limited	Yes	Unclear or NR Medication adherence outcomes broadly applicable, but morbidity outcomes of varying significance, appear to be post-hoc; too numerous to report all in this table, most relevant to med adherence chosen.
Stacy et al., 2009[56] NA	No After randomization, those that had no intention of picking up medication, not aware of statin prescription, or failed to answer at least 50% of baseline assessment	No seems this intervention could only be made available to MCO participants	Yes	Yes
Taylor et al., 2003[57] NA	No Eligibility criteria were narrow, but it is possible that this sample is broadly applicable in terms of high-risk patients	Yes	No No attention-matched control	No 80% adherence cut-off may not be applicable for all diseases
Vivian et al., 2002[58] NA	No VA medical center patients only; excluded if missed more than 3 appointments	No Ability for pharmacist to do this and have prescribing authority is limited to VA system; outside the VA system, pharmacists currently only have the potential for prescribing authority as Clinical Pharmacist Practitioners in 2 states (NC and New Mexico)	Yes	No Short term adherence measured only (6 months); measure was not validated
Waalen et al., 2009[59] NA	Yes	Yes	No There was no attention-matched control condition, and very little was reported about receipt of care in the control arm.	No The outcome is "use of medications" rather than "medication adherence."

Author, Year Trial Name	Is the study population broadly applicable? Comments if "no" response	Is the intervention broadly applicable? Comments if "no" response	Is the comparator broadly applicable? Comments if "no" response	Are the outcomes broadly applicable? Comments if "no" response
Wakefield et al., 2011[60] NA	No limited to VA patients	No intervention seems very labor intensive so unsure of how feasible it would be to do this in a setting outside the VA	Yes	No no clear measure of medication adherence, only measured on a scale where medication adherence is only one question and the others have to do with diet, exercise, glucose monitoring, and etc.
Weinberger et al., 2002[61] NA	Yes	Yes	Yes	Yes
Weymiller et al., 2007[62] Statin Choice Randomized Trial Jones et al., 2009[63] Statin Choice Randomized Trial	No Study patients more educated than community patients, and were recruited in a specialty clinic as opposed to a primary care clinic	Yes	Yes	Yes
Williams et al., 2010[64] NA	Yes	Yes	Yes	Yes
Wilson et al., 2010[65] Better Outcomes of Asthma Treatment (BOAT); note that there is online supplemental material for methods and timeline	Yes	Yes	Yes	Yes

Author, Year Trial Name	Is the study population broadly applicable? Comments if "no" response	Is the intervention broadly applicable? Comments if "no" response	Is the comparator broadly applicable? Comments if "no" response	Are the outcomes broadly applicable? Comments if "no" response
Wolever et al., 2010[66] NA	Yes	Unclear or NR	Yes	Yes
Zhang et al., 2010[67] NA	Yes	Yes	No Comparison group was a group of elderly patients receiving retiree health benefits; this is a narrowly defined population	Yes

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Appendix E. Risk of Bias Tables

Table E1. Risk of bias ratings, part 1

Author, Year Trial name	Method of randomization adequate?	Allocation of treatment adequately concealed?	Did strategy for recruiting participants into study differ across study groups?	Baseline characteristics similar between groups? If not, did analysis control for differences?	Were providers blinded to intervention or exposure status of participants?
Babamoto et al., 2009[1] NR	Yes	Unclear or NR	No	No	No
Bender et al., 2010[2] NA	Yes	Yes	No	Yes	Yes
Berg et al., 1997[3] NA	Unclear or NR	Unclear or NR	No	Yes	Unclear or NR
Berger et al., 2005[4] NA	Yes	Unclear or NR	No	Yes	Unclear or NR
Bogner et al., 2008[5] NA	Unclear or NR	Unclear or NR	No	Yes	No
Bogner et al., 2010[6] NA	Unclear or NR	Unclear or NR	No	Yes	No
Bosworth et al., 2005[7] V-STITCH	Yes	Yes	No	Yes	No
Bosworth et al., 2008[8] TCYB Bosworth et al., 2007[9] TCYB Methods paper	Yes	Unclear or NR	No	Yes	Unclear or NR
Brown et al., 2008[10]	Unclear or NR	Yes	Yes	No	Unclear or NR
Capoccia et al., 2004[11] NA	Yes	Unclear or NR	No	Yes	No

Author, Year Trial name	Method of randomization adequate?	Allocation of treatment adequately concealed?	Did strategy for recruiting participants into study differ across study groups?	Baseline characteristics similar between groups? If not, did analysis control for differences?	Were providers blinded to intervention or exposure status of participants?
Carter et al., 2008[12] NA	Yes	Unclear or NR	No	No	Unclear or NR
Carter et al., 2009[13] NA	Yes	Unclear or NR	No	No	No
Chernew et al., 2008[14] NA	NA	NA	No	No	NA
Choudhry et al., 2010[15] NA	No	NA	Yes	No	No
Choudhry et al., 2011[16] MI FREEE	Unclear or NR	Unclear or NR	No	yes	Unclear or NR
Esposito et al., 1995[17] NA	Yes	Yes	No	No	Unclear or NR
Fortney et al., 2007[18] TEAM (Telemedicine Enhanced Antidepressant Management)	Unclear or NR	Unclear or NR	No	Yes	No
Friedman et al., 1996[19] NA	Unclear or NR	Unclear or NR	No	Yes	Yes
Fulmer et al., 1999[20] NA	Yes	Unclear or NR	No	Yes	Unclear or NR
Grant et al., 2003[21] NA	Yes	Unclear or NR	No	Yes	No
Guthrie et al., 2001[22] First Myocardial Infarction (MI) Risk Reduction Program	Unclear or NR	Unclear or NR	No	Yes	Unclear or NR

Author, Year Trial name	Method of randomization adequate?	Allocation of treatment adequately concealed?	Did strategy for recruiting participants into study differ across study groups?	Baseline characteristics similar between groups? If not, did analysis control for differences?	Were providers blinded to intervention or exposure status of participants?
Hoffman et al., 2003[23] NA	No	No	No	Yes	No
Hunkeler, et al., 2000[24]	Unclear or NR	Unclear or NR	No	Unclear or NR	Unclear or NR
Hunt et al., 2008[25] NA	Yes	Unclear or NR	No	Yes	No
Janson et al., 2003[26] NA	Unclear or NR	Unclear or NR	No	Yes	Yes
Janson et al., 2010[27] NA	Unclear or NR	Unclear or NR	No	Yes	No
Janson et al., 2009[28] NA	Yes	Unclear or NR	No	Yes	Yes
Johnson et al., 2006[29] NR	Unclear or NR	Unclear or NR	No	No	Unclear or NR
Johnson et al., 2006[30] NR	Unclear or NR	Unclear or NR	Unclear or NR	Unclear or NR	Unclear or NR
Johnston et al., 2000[31] NA	Unclear or NR	Unclear or NR	Unclear or NR	No	No
Katon et al., 1995[32] NA	Yes	Unclear or NR	No	Yes	No
Katon et al., 1996[33] NA	Yes	Yes	No	Yes	No
Katon et al., 1999[34] NA Katon et al., 2002[35] NA	Yes	Unclear or NR	No	Yes	No

Author, Year Trial name	Method of randomization adequate?	Allocation of treatment adequately concealed?	Did strategy for recruiting participants into study differ across study groups?	Baseline characteristics similar between groups? If not, did analysis control for differences?	Were providers blinded to intervention or exposure status of participants?
Katon et al., 2001[36] NA Ludman et al., 2003[37] NA Van Korff et al., 2003[38] NA	Yes	Unclear or NR	No	Yes	No
Katon et al., 2004[39] Pathways	Yes	Unclear or NR	No	Yes	No
Laramee et al., 2003[40] NA	No	Unclear or NR	No	No	No
Lee et al., 2006[41] FAME	Yes	Yes	No	Yes	No
Lin et al., 2006[42] NA	Yes	Unclear or NR	No	Yes	No
Maciejewski et al., 2010[43] NA	NA	NA	No	Yes	NA
Mann et al., 2010[44] The Statin Choice	Unclear or NR	Unclear or NR	Unclear or NR	Yes	No
Martin et al., 2011[45] HARP	Yes	Unclear or NR	No	Yes	Unclear or NR
Montori et al., 2011[46] NA	Yes	Yes	No	No	Unclear or NR
Mundt et al., 2001[47] NA	Yes	Yes	No	Yes	Unclear or NR

Author, Year Trial name	Method of randomization adequate?	Allocation of treatment adequately concealed?	Did strategy for recruiting participants into study differ across study groups?	Baseline characteristics similar between groups? If not, did analysis control for differences?	Were providers blinded to intervention or exposure status of participants?
Murray et al., 2007[48] NA	Yes	Yes	No	Yes	No
Nietert et al., 2009[49] NA	Yes	Yes	No	Yes	No
Odegard et al., 2005[50] NA	Unclear or NR	Unclear or NR	No	Yes	No
Okeke et al., 2009[51] NA	Yes	Yes	No	Yes	Unclear or NR
Park et al., 1996[52] NA	Unclear or NR	Unclear or NR	No	No	no
Pearce et al., 2008[53] Cardiovascular Risk Education and Social Support (CaRESS) Trial	Yes	Yes	No	Unclear or NR	Unclear or NR
Planas et al., 2009[54] NR	Yes	Unclear or NR	No	No	No
Powell et al., 1995[55] NA	Unclear or NR	Unclear or NR	No	Yes	NA
Powers et al., 2011[56] NA	Unclear or NR	Unclear or NR	No	No	Unclear or NR
Pyne et al., 2011[57] HIV Translating Initiatives for Depression Into Effective Solutions (HITIDES)	Yes	Yes	No	Yes	No

Author, Year Trial name	Method of randomization adequate?	Allocation of treatment adequately concealed?	Did strategy for recruiting participants into study differ across study groups?	Baseline characteristics similar between groups? If not, did analysis control for differences?	Were providers blinded to intervention or exposure status of participants?
Rich et al., 1996[58] NA	Yes	Yes	No	No	No
Rickles et al., 2005[59] NA	Unclear or NR	Unclear or NR	No	No	No
Rodin et al., 2009[60] NA	NA	No	Yes	No	NA
Ross et al., 2004[61] NR	Yes	Unclear or NR	No	Yes	No
Rudd et al., 2004[62] NA	Yes	Unclear or NR	No	Yes	No
Rudd et al., 2009[63] NA	Unclear or NR	Unclear or NR	No	Yes	Yes
Ruskin et al., 2004[64] NA	Yes	Unclear or NR	No	Yes	No
Schaffer et al., 2004[65] NA	Yes	Unclear or NR	No	Yes	Yes
Schectman et al., 1994[66] NA	Unclear or NR	Unclear or NR	No	Yes	Yes
Schneider et al., 2008[67] NA	Yes	Yes	No	Yes	Yes
Schnipper et al., 2006[68] NA	Yes	Yes	No	Yes	No
Shu et al., 2009[69] NA	Unclear or NR	Unclear or NR	Unclear or NR	Yes	No
Simon et al., 2006[70] NA	Yes	Yes	No	Yes	No

Author, Year Trial name	Method of randomization adequate?	Allocation of treatment adequately concealed?	Did strategy for recruiting participants into study differ across study groups?	Baseline characteristics similar between groups? If not, did analysis control for differences?	Were providers blinded to intervention or exposure status of participants?
Sledge et al., 2006[71] NA	Yes	Yes	No	Yes	No
Smith et al., 2008[72] NR	Yes	No	No	Yes	No
Solomon et al., 1998[73] NA Gourley et al., 1998[74] NA	Yes	No	Unclear or NR	No	No
Stacy et al., 2009[75] NA	Unclear or NR	Unclear or NR	No	No	NA
Stuart et al., 2003[76] NA	Unclear or NR	Unclear or NR	Unclear or NR	Unclear or NR	No
Taylor et al., 2003[77] NA	Unclear or NR	Unclear or NR	No	Yes	Unclear or NR
Vivian et al., 2002[78] NA	Unclear or NR	Unclear or NR	No	No	No
Waalen et al., 2009[79] NA	Yes	Unclear or NR	No	Yes	No
Wakefield et al., 2008[80]	Yes	Yes	No	No	Unclear or NR
Wakefield et al., 2009[81] NA	Yes	Yes	No	No	Unclear or NR
Wakefield et al., 2011[82] NA	Unclear or NR	Yes	No	Yes	No
Weinberger et al., 2002[83] NA	Yes	Unclear or NR	No	Yes	No

Author, Year Trial name	Method of randomization adequate?	Allocation of treatment adequately concealed?	Did strategy for recruiting participants into study differ across study groups?	Baseline characteristics similar between groups? If not, did analysis control for differences?	Were providers blinded to intervention or exposure status of participants?
Weymiller et al., 2007[84] Statin Choice Randomized Trial Jones et al., 2009[85] Statin Choice Randomized Trial	Yes	Yes	No	Yes	Yes
Williams et al., 2004[86] IMPACT (Improving Mood–Promoting Access to Collaborative Treatment)	Yes	Yes	No	Yes	No
Williams et al., 2010[87] NA	Unclear or NR	Yes	No	Yes	No
Wilson et al., 2010[88] Better Outcomes of Asthma Treatment (BOAT); note that there is online supplemental material for methods and timeline	Yes	Yes	No	Yes	No
Wolever et al., 2010[89] NA	Unclear or NR	Yes	No	Yes	No

Author, Year Trial name	Method of randomization adequate?	Allocation of treatment adequately concealed?	Did strategy for recruiting participants into study differ across study groups?	Baseline characteristics similar between groups? If not, did analysis control for differences?	Were providers blinded to intervention or exposure status of participants?
Zeng et al., 2010[90] NA	No	Unclear or NR	No	No	NA
Zhang et al., 2010[91] NA	NA	No	Yes	Yes	NA

Table E2. Risk of bias ratings, part 2

Author, Year Trial name	Participants blinded to intervention or exposure status?	Outcome assessors blinded to intervention or exposure status of participants?	Impact from any concurrent intervention or unintended exposure that might bias results ruled out?	Did variation from study protocol compromise study conclusions?	High rate of differential or overall attrition?	Did attrition result in difference in group characteristics between baseline (or randomization) and follow-up?
Babamoto et al., 2009[1] NR	No	Unclear or NR	Unclear or NR	No	Yes	Unclear or NR
Bender et al., 2010[2] NA	Unclear or NR	Yes	Yes	Unclear or NR	No	No
Berg et al., 1997[3] NA	Unclear or NR	Unclear or NR	Unclear or NR	Unclear or NR	No	No
Berger et al., 2005[4] NA	No	Unclear or NR	No	No	No	No
Bogner et al., 2008[5] NA	No	Unclear or NR	Unclear or NR	Unclear or NR	No	No
Bogner et al., 2010[6] NA	Unclear or NR	Unclear or NR	Yes	Unclear or NR	No	No
Bosworth et al., 2005[7] V-STITCH	No	Unclear or NR	Unclear or NR	Unclear or NR	Unclear or NR	Unclear or NR
Bosworth et al., 2008[8] TCYB Bosworth et al., 2007[9] TCYB Methods paper	No	Unclear or NR	Unclear or NR	No	Unclear or NR	Unclear or NR
Brown et al., 2008[10]	No	Unclear or NR	No	Unclear or NR	Unclear or NR	Unclear or NR
Capoccia et al., 2004[11] na	No	Unclear or NR	Unclear or NR	Unclear or NR	No	Unclear or NR
Carter et al., 2008[12] NA	Unclear or NR	Unclear or NR	Unclear or NR	Unclear or NR	No	No

Author, Year Trial name	Participants blinded to intervention or exposure status?	Outcome assessors blinded to intervention or exposure status of participants?	Impact from any concurrent intervention or unintended exposure that might bias results ruled out?	Did variation from study protocol compromise study conclusions?	High rate of differential or overall attrition?	Did attrition result in difference in group characteristics between baseline (or randomization) and follow-up?
Carter et al., 2009[13] NA	Unclear or NR	Unclear or NR	Unclear or NR	Unclear or NR	No	No
Chernew et al., 2008[14] NA	NA	No	Yes	No	Unclear or NR	Unclear or NR
Choudhry et al., 2010[15] NA	No	Unclear or NR	No	No	No	No
Choudhry et al., 2011[16] MI FREEE	No	unclear or NR	No	No	No	NA
Esposito et al., 1995[17] NA	no	no	no	no	No	Unclear or NR
Fortney et al., 2007[18] TEAM (Telemedicine Enhanced Antidepressant Management)	Unclear or NR	Yes	Unclear or NR	Unclear or NR	No	Unclear or NR
Friedman et al., 1996[19] NA	No	Yes	Unclear or NR	No	No	No
Fulmer et al., 1999[20] NA	No	No	No	No	No	No
Gould et al., 2011[92]	No	Unclear or NR	No	No	Unclear or NR	Unclear or NR
Guthrie et al., 2001[22] First Myocardial Infarction (MI) Risk Reduction Program	No	Unclear or NR	Yes	No	Yes	Unclear or NR

Author, Year Trial name	Participants blinded to intervention or exposure status?	Outcome assessors blinded to intervention or exposure status of participants?	Impact from any concurrent intervention or unintended exposure that might bias results ruled out?	Did variation from study protocol compromise study conclusions?	High rate of differential or overall attrition?	Did attrition result in difference in group characteristics between baseline (or randomization) and follow-up?
Hoffman et al., 2003[23] NA	No	Unclear or NR	Unclear or NR	No	No	No
Hunkeler, et al., 2000[24]	Unclear or NR	Unclear or NR	No	Unclear or NR	No	NA
Hunt et al., 2008[25] NA	No	Yes	No	No	Yes	Unclear or NR
Janson et al., 2003[26] NA	Yes	Unclear or NR	Unclear or NR	Unclear or NR	No	NA
Janson et al., 2010[27] NA	Yes	Yes	Unclear or NR	No	No	Unclear or NR
Janson et al., 2009[28] NA	Unclear or NR	Yes	Unclear or NR	Unclear or NR	No	No
Johnson et al., 2006[29] NR	Unclear or NR	Unclear or NR	No	Unclear or NR	Yes	Unclear or NR
Johnson et al., 2006[30] NR	Unclear or NR	Unclear or NR	No	Unclear or NR	Yes	Unclear or NR
Johnston et al., 2000[31] NA	Unclear or NR	Unclear or NR	No	Unclear or NR	Unclear or NR	Unclear or NR
Katon et al., 1995[32] NA	No	Yes	Unclear or NR	Unclear or NR	No	No
Katon et al., 1996[33] NA	No	Unclear or NR	Unclear or NR	No	Unclear or NR	Unclear or NR

Author, Year Trial name	Participants blinded to intervention or exposure status?	Outcome assessors blinded to intervention or exposure status of participants?	Impact from any concurrent intervention or unintended exposure that might bias results ruled out?	Did variation from study protocol compromise study conclusions?	High rate of differential or overall attrition?	Did attrition result in difference in group characteristics between baseline (or randomization) and follow-up?
Katon et al., 1999[34] NA Katon et al., 2002[35] NA	Unclear or NR	Yes	Unclear or NR	Unclear or NR	Unclear or NR	Unclear or NR
Katon et al., 2001[36] NA Ludman et al., 2003[37] NA Van Korff et al., 2003[38] NA	No	Yes	No	Unclear or NR	No	Unclear or NR
Katon et al., 2004[39] Pathways	Unclear or NR	Yes	No	Unclear or NR	No	Unclear or NR
Laramee et al., 2003[40] NA	No	Unclear or NR	Unclear or NR	No	Yes	Unclear or NR
Lee et al., 2006[41] FAME	No	No	Yes	No	No	No
Lin et al., 2006[42] NA	No	Unclear or NR	Yes	No	No	No
Maciejewski et al., 2010[43] NA	NA	NA	Yes	No	Unclear or NR	Unclear or NR
Mann et al., 2010[44] The Statin Choice	No	Unclear or NR	Unclear or NR	Unclear or NR	Unclear or NR	Unclear or NR
Martin et al., 2011[45] HARP	No	Unclear or NR	Unclear or NR	Unclear or NR	Yes	Unclear or NR

Author, Year Trial name	Participants blinded to intervention or exposure status?	Outcome assessors blinded to intervention or exposure status of participants?	Impact from any concurrent intervention or unintended exposure that might bias results ruled out?	Did variation from study protocol compromise study conclusions?	High rate of differential or overall attrition?	Did attrition result in difference in group characteristics between baseline (or randomization) and follow-up?
Montori et al., 2011[46] NA	No	Yes	No	No	No	NA
Mundt et al., 2001[47] NA	No	NA	Unclear or NR	No	Yes	Unclear or NR
Murray et al., 2007[48] NA	Unclear or NR	Unclear or NR	Unclear or NR	No	No	No
Nietert et al., 2009[49] NA	No	Unclear or NR	Yes	Unclear or NR	No	No
Odegard et al., 2005[50] NA	No	Unclear or NR	Unclear or NR	No	Yes	Unclear or NR
Okeke et al., 2009[51] NA	No	Unclear or NR	Unclear or NR	Unclear or NR	No	No
Park et al., 1996[52] NA	no	no	No	No	No	Unclear or NR
Pearce et al., 2008[53] Cardiovascular Risk Education and Social Support (CaRESS) Trial	Yes	Unclear or NR	Yes	Unclear or NR	No	Unclear or NR
Planas et al., 2009[54] NR	No	Unclear or NR	No	No	Yes	Unclear or NR
Powell et al., 1995[55] NA	Yes	Unclear or NR	No	Unclear or NR	No	No
Powers et al., 2011[56] NA	No	Unclear or NR	Unclear or NR	No	No	No

Author, Year Trial name	Participants blinded to intervention or exposure status?	Outcome assessors blinded to intervention or exposure status of participants?	Impact from any concurrent intervention or unintended exposure that might bias results ruled out?	Did variation from study protocol compromise study conclusions?	High rate of differential or overall attrition?	Did attrition result in difference in group characteristics between baseline (or randomization) and follow-up?
Pyne et al., 2011[57] HIV Translating Initiatives for Depression Into Effective Solutions (HITIDES)	Unclear or NR	Yes	Unclear or NR	Unclear or NR	Yes	Unclear or NR
Rich et al., 1996[58] NA	No	Yes	No	No	No	No
Rickles et al., 2005[59] NA	No	No	Unclear or NR	Unclear or NR	No	Unclear or NR
Rodin et al., 2009[60] NA	No	NA	Unclear or NR	No	No	No
Ross et al., 2004[61] NR	No	Unclear or NR	Unclear or NR	No	Yes	Unclear or NR
Rudd et al., 2004[62] NA	Unclear or NR	Yes	Unclear or NR	No	No	Unclear or NR
Rudd et al., 2009[63] NA	No	Unclear or NR	No	Unclear or NR	No	NA
Ruskin et al., 2004[64] NA	Unclear or NR	Unclear or NR	Unclear or NR	Unclear or NR	Yes	Unclear or NR
Schaffer et al., 2004[65] NA	No	Yes	Unclear or NR	Unclear or NR	No	No
Schectman et al., 1994[66] NA	No	Unclear or NR	No	No	Yes	Unclear or NR
Schneider et al., 2008[67] NA	No	Unclear or NR	No	No	No	No
Schnipper et al., 2006[68] NA	No	Yes	No	No	No	No
Shu et al., 2009[69] NA	No	Unclear or NR	No	Unclear or NR	Unclear or NR	Unclear or NR

Author, Year Trial name	Participants blinded to intervention or exposure status?	Outcome assessors blinded to intervention or exposure status of participants?	Impact from any concurrent intervention or unintended exposure that might bias results ruled out?	Did variation from study protocol compromise study conclusions?	High rate of differential or overall attrition?	Did attrition result in difference in group characteristics between baseline (or randomization) and follow-up?
Simon et al., 2006[70] NA	No	Yes	Unclear or NR	Unclear or NR	No	Unclear or NR
Sledge et al., 2006[71] NA	No	Unclear or NR	No	No	No	No
Smith et al., 2008[72] NR	No	Yes	Unclear or NR	Yes	No	No
Solomon et al., 1998[73] NA Gourley et al., 1998[74] NA	No	No	Unclear or NR	No	Unclear or NR	Unclear or NR
Stacy et al., 2009[75] NA	No	Unclear or NR	No	No	No	No
Stuart et al., 2003[76] NA	No	Unclear or NR	No	Unclear or NR	Yes	Unclear or NR
Taylor et al., 2003[77] NA	No	Unclear or NR	No	No	No	No
Vivian et al., 2002[78] NA	No	Unclear or NR	Unclear or NR	No	No	No
Waalen et al., 2009[79] NA	No	Unclear or NR	No	No	No	Unclear or NR
Wakefield et al., 2008[80]	No	Unclear or NR	Unclear or NR	Yes	Yes	Unclear or NR
Wakefield et al., 2009[81] NA	No	Unclear or NR	Unclear or NR	Yes	Yes	Unclear or NR

Author, Year Trial name	Participants blinded to intervention or exposure status?	Outcome assessors blinded to intervention or exposure status of participants?	Impact from any concurrent intervention or unintended exposure that might bias results ruled out?	Did variation from study protocol compromise study conclusions?	High rate of differential or overall attrition?	Did attrition result in difference in group characteristics between baseline (or randomization) and follow-up?
Wakefield et al., 2011[82] NA	No	NA	Unclear or NR	Unclear or NR	Yes	Unclear or NR
Weinberger et al., 2002[83] NA	Unclear or NR	Yes	Unclear or NR	No	No	NA
Weymiller et al., 2007[84] Statin Choice Randomized Trial Jones et al., 2009[85] Statin Choice Randomized Trial	Yes	Yes	No	Unclear or NR	No	No
Williams et al., 2004[86] IMPACT (Improving Mood–Promoting Access to Collaborative Treatment)	No	Yes	Unclear or NR	Unclear or NR	No	Unclear or NR
Williams et al., 2010[87] NA	Unclear or NR	Unclear or NR	Unclear or NR	No	No	Unclear or NR
Wilson et al., 2010[88] Better Outcomes of Asthma Treatment (BOAT); note that there is online supplemental material for methods and timeline	Unclear or NR	Unclear or NR	Unclear or NR	No	No	Unclear or NR

Author, Year Trial name	Participants blinded to intervention or exposure status?	Outcome assessors blinded to intervention or exposure status of participants?	Impact from any concurrent intervention or unintended exposure that might bias results ruled out?	Did variation from study protocol compromise study conclusions?	High rate of differential or overall attrition?	Did attrition result in difference in group characteristics between baseline (or randomization) and follow-up?
Wolever et al., 2010[89] NA	No	Yes	No	Unclear or NR	No	No
Zeng et al., 2010[90] NA	No	NA	Unclear or NR	No	No	No
Zhang et al., 2010[91] NA	No	NA	Unclear or NR	No	No	No

Table E3. Risk of bias ratings, part 3

Author, Year Trial name	Analysis conducted on an intention-to-treat (ITT) basis?	Inclusion/exclusion criteria measured using valid and reliable measures, implemented consistently across all study participants?	Medication adherence outcomes assessed using valid and reliable measures, implemented consistently across all study participants? When adherence requires skills (e.g., eye drop use), does the intervention measure or account for varied skill levels?	Do authors justify medication adherence thresholds?	Are health outcomes assessed using valid and reliable measures, implemented consistently across all study participants?
Babamoto et al., 2009[1] NR	Unclear or NR	Yes	No	NA	NA
Bender et al., 2010[2] NA	Yes	Unclear or NR	Yes	NA	Yes
Berg et al., 1997[3] NA	Yes	Unclear or NR	Yes	NA	Yes
Berger et al., 2005[4] NA	No	Yes	No	NA	NA
Bogner et al., 2010[6] NA	Yes	Yes	Yes	Yes	Yes
Bogner et al., 2008[5] NA	NA	Unclear or NR	Yes	Yes	Yes
Bosworth et al., 2005[7] V-STITCH	Unclear or NR	Yes	Yes	Yes	NA
Bosworth et al., 2008[8] TCYB Bosworth et al., 2007[9] TCYB Methods paper	Unclear or NR	Unclear or NR	Yes	Yes	NA
Brown et al., 2008[10]	Yes	No	No	NA	NA
Capoccia et al., 2004[11] NA	Yes	Yes	No	No	Yes

Author, Year Trial name	Analysis conducted on an intention-to-treat (ITT) basis?	Inclusion/exclusion criteria measured using valid and reliable measures, implemented consistently across all study participants?	Medication adherence outcomes assessed using valid and reliable measures, implemented consistently across all study participants? When adherence requires skills (e.g., eye drop use), does the intervention measure or account for varied skill levels?	Do authors justify medication adherence thresholds?	Are health outcomes assessed using valid and reliable measures, implemented consistently across all study participants?
Carter et al., 2008[12] NA	Yes	Unclear or NR	Yes	NA	Unclear or NR
Carter et al., 2009[13] NA	Yes	Unclear or NR	No	Yes	Yes
Chernew et al., 2008[14] NA	No	Yes	Yes	Yes	NA
Choudhry et al., 2010[15] NA	Yes	Unclear or NR	Yes	Yes	NA
Choudhry et al., 2011[16] MI FREEE	Yes	Yes	Yes	NA	Yes
Esposito et al., 1995[17] NA	No	Yes	Yes	NA	NA
Fortney et al., 2007[18] TEAM (Telemedicine Enhanced Antidepressant Management)	Yes	Yes	No	No	Yes
Friedman et al., 1996[19] NA	No	Yes	Yes	NA	Yes
Fulmer et al., 1999[20] NA	No	Yes	Yes	NA	Yes
Gould et al., 201192	No	Unclear or NR	Yes	NA	NA
Grant et al., 2003[21] NA	No	Yes	No	NA	NA

Author, Year Trial name	Analysis conducted on an intention-to-treat (ITT) basis?	Inclusion/exclusion criteria measured using valid and reliable measures, implemented consistently across all study participants?	Medication adherence outcomes assessed using valid and reliable measures, implemented consistently across all study participants? When adherence requires skills (e.g., eye drop use), does the intervention measure or account for varied skill levels?	Do authors justify medication adherence thresholds?	Are health outcomes assessed using valid and reliable measures, implemented consistently across all study participants?
Guthrie et al., 2001[22] First Myocardial Infarction (MI) Risk Reduction Program	No	Unclear or NR	No	No	NA
Hoffman et al., 2003[23] NA	Yes	Yes	Yes	Yes	NA
Hunkeler, et al., 200024	No	Unclear or NR	Yes	NA	Yes
Hunt et al., 2008[25] NA	No	Yes	No	Unclear or NR	Yes
Janson et al., 2003[26] NA	Unclear or NR	Yes	Yes	NA	Yes
Janson et al., 2009[28] NA	Yes	Yes	Yes	NA	No
Janson et al., 2010[27] NA	Yes	Yes	Yes	No	No
Johnson et al., 2006[30] NR	Unclear or NR	Yes	No	Unclear or NR	NA
Johnson et al., 2006[29] NR	Unclear or NR	Yes	No	No	NA
Johnston et al., 2000[31] NA	No	No	Unclear or NR	NA	NA
Katon et al., 1996[33] NA	Unclear or NR	Yes	Yes	Yes	Yes

Author, Year Trial name	Analysis conducted on an intention-to-treat (ITT) basis?	Inclusion/exclusion criteria measured using valid and reliable measures, implemented consistently across all study participants?	Medication adherence outcomes assessed using valid and reliable measures, implemented consistently across all study participants? When adherence requires skills (e.g., eye drop use), does the intervention measure or account for varied skill levels?	Do authors justify medication adherence thresholds?	Are health outcomes assessed using valid and reliable measures, implemented consistently across all study participants?
Katon et al., 2001[36] NA Ludman et al., 2003[37] NA Van Korff et al., 2003[38] NA	No	Yes	Yes	Yes	Yes
Katon et al., 2004[39] Pathways	Yes	Yes	No	No	Yes
Katon et al., 1995[32] NA	No	Yes	Yes	Yes	Yes
Katon et al., 1999[34] NA Katon et al., 2002[35] NA	Yes	Yes	Yes	Unclear or NR	Yes
Laramee et al., 2003[40] NA	Unclear or NR	Yes	No	No	NA
Lee et al., 2006[41] FAME	Yes	Yes	Unclear or NR	No	Yes
Lin et al., 2006[42] NA	Unclear or NR	Yes	Yes	NA	Unclear or NR
Maciejewski et al., 2010[43] NA	Unclear or NR	Yes	Yes	NA	NA

Author, Year Trial name	Analysis conducted on an intention-to-treat (ITT) basis?	Inclusion/exclusion criteria measured using valid and reliable measures, implemented consistently across all study participants?	Medication adherence outcomes assessed using valid and reliable measures, implemented consistently across all study participants? When adherence requires skills (e.g., eye drop use), does the intervention measure or account for varied skill levels?	Do authors justify medication adherence thresholds?	Are health outcomes assessed using valid and reliable measures, implemented consistently across all study participants?
Mann et al., 2010[44] The Statin Choice	Unclear or NR	Unclear or NR	No	Unclear or NR	Yes
Martin et al., 2011[45] HARP	No	Unclear or NR	Yes	No	NA
Montori et al., 2011[46] NA	Yes	Yes	Yes	No	NA
Mundt et al., 2001[47] NA	No	Yes	Yes	NA	Yes
Murray et al., 2007[48] NA	Yes	Yes	Yes	NA	Yes
Nietert et al., 2009[49] NA	Yes	Yes	Unclear or NR	NA	NA
Odegard et al., 2005[50] NA	Yes	Yes	No	Unclear or NR	Yes
Okeke et al., 2009[51] NA	Yes	Yes	Yes	No	Yes
Park et al., 1996[52] NA	Unclear or NR	Yes	Yes	NA	Yes
Pearce et al., 2008[53] Cardiovascular Risk Education and Social Support (CaRESS) Trial	Unclear or NR	Yes	No	Unclear or NR	Yes

Author, Year Trial name	Analysis conducted on an intention-to-treat (ITT) basis?	Inclusion/exclusion criteria measured using valid and reliable measures, implemented consistently across all study participants?	Medication adherence outcomes assessed using valid and reliable measures, implemented consistently across all study participants? When adherence requires skills (e.g., eye drop use), does the intervention measure or account for varied skill levels?	Do authors justify medication adherence thresholds?	Are health outcomes assessed using valid and reliable measures, implemented consistently across all study participants?
Planas et al., 2009[54] NR	Yes	Yes	Yes	NA	Yes
Powell et al., 1995[55] NA	Yes	Unclear or NR	Yes	Yes	NA
Powers et al., 2011[56] NA	Yes	Yes	No	NA	NA
Pyne et al., 2011[57] HIV Translating Initiatives for Depression Into Effective Solutions (HITIDES)	Yes	Yes	No	Yes	Yes
Rich et al., 1996[58] NA	Yes	No	Yes	No	Unclear or NR
Rickles et al., 2005[59] NA	Yes	Yes	Yes	NA	Yes
Rodin et al., 2009[60] NA	Yes	Yes	Yes	No	NA
Ross et al., 2004[61] NR	Unclear or NR	Yes	No	Yes	Unclear or NR
Rudd et al., 2004[62] NA	Unclear or NR	Yes	Yes	Yes	Yes
Rudd et al., 2009[63] NA	Unclear or NR	Unclear or NR	No	NA	NA

Author, Year Trial name	Analysis conducted on an intention-to-treat (ITT) basis?	Inclusion/exclusion criteria measured using valid and reliable measures, implemented consistently across all study participants?	Medication adherence outcomes assessed using valid and reliable measures, implemented consistently across all study participants? When adherence requires skills (e.g., eye drop use), does the intervention measure or account for varied skill levels?	Do authors justify medication adherence thresholds?	Are health outcomes assessed using valid and reliable measures, implemented consistently across all study participants?
Ruskin et al., 2004[64] NA	No	Yes	Yes	No	NA
Schaffer et al., 2004[65] NA	Unclear or NR	No	Yes	NA	Yes
Schectman et al., 1994[66] NA	No	Unclear or NR	Yes	NA	NA
Schneider et al., 2008[67] NA	No	Unclear or NR	Yes	NA	Yes
Schnipper et al., 2006[68] NA	No	yes	Yes	No	NA
Shu et al., 2009[69] NA	Yes	Unclear or NR	No	NA	NA
Simon et al., 2006[70] NA	Yes	Yes	Yes	Unclear or NR	Yes
Sledge et al., 2006[71] NA	No	Yes	No	NA	NA
Smith et al., 2008[72] NR	Yes	Yes	Yes	Yes	NA
Solomon et al., 1998[73] NA Gourley et al., 1998[74] NA	Unclear or NR	Yes	Yes	No	Unclear or NR
Stacy et al., 2009[75] NA	No	No	Yes	Yes	NA

Author, Year Trial name	Analysis conducted on an intention-to-treat (ITT) basis?	Inclusion/exclusion criteria measured using valid and reliable measures, implemented consistently across all study participants?	Medication adherence outcomes assessed using valid and reliable measures, implemented consistently across all study participants? When adherence requires skills (e.g., eye drop use), does the intervention measure or account for varied skill levels?	Do authors justify medication adherence thresholds?	Are health outcomes assessed using valid and reliable measures, implemented consistently across all study participants?
Stuart et al., 2003[76] NA	Unclear or NR	Unclear or NR	No	No	NA
Taylor et al., 2003[77] NA	No	yes	No	No	NA
Vivian et al., 2002[78] NA	No	Yes	No	No	NA
Waalen et al., 2009[79] NA	Yes	Unclear or NR	Yes	No	NA
Wakefield et al., 2008[80] NA	Unclear or NR	Yes	No	Unclear or NR	NA
Wakefield et al., 2009[81] NA	Unclear or NR	Yes	No	Unclear or NR	NA
Wakefield et al., 2011[82] NA	Yes	Yes	No	Unclear or NR	NA
Weinberger et al., 2002[83] NA	Yes	Yes	No	NA	Yes
Weymiller et al., 2007[84] Statin Choice Randomized Trial Jones et al., 2009[85] Statin Choice Randomized Trial	Yes	Unclear or NR	No	NA	NA

Author, Year Trial name	Analysis conducted on an intention-to-treat (ITT) basis?	Inclusion/exclusion criteria measured using valid and reliable measures, implemented consistently across all study participants?	Medication adherence outcomes assessed using valid and reliable measures, implemented consistently across all study participants? When adherence requires skills (e.g., eye drop use), does the intervention measure or account for varied skill levels?	Do authors justify medication adherence thresholds?	Are health outcomes assessed using valid and reliable measures, implemented consistently across all study participants?
Williams et al., 2004[86] IMPACT (Improving Mood–Promoting Access to Collaborative Treatment)	Yes	Yes	No	No	Yes
Williams et al., 2010[87] NA	Yes	Yes	Yes	NA	Yes
Wilson et al., 2010[88] Better Outcomes of Asthma Treatment (BOAT); note that there is online supplemental material for methods and timeline	No	Yes	Yes	NA	Yes
Wolever et al., 2010[89] NA	No	Yes	No	Unclear or NR	Yes
Zeng et al., 2010[90] NA	Yes	Yes	Yes	Yes	NA
Zhang et al., 2010[91] NA	Yes	Yes	Yes	Yes	NA

Table E4. Risk of bias ratings, part 4

Author, Year Trial name	Harms assessed using valid and reliable measures, implemented consistently across all study participants?	Potential outcomes pre-specified by researchers? Are all pre-specified outcomes reported?	[For observational studies only] Important confounding and modifying variables taken into account in the design and/or analysis?	Risk of bias	Comments
Babamoto et al., 2009[1] NR	NA	No	NA	High	Higher rates of attrition in standard care (50%) and case management(43%) groups compared to CHW group (28%); could be the reason why adherence worsened in standard care and case management groups; differences in groups at baseline, no blinding, single-question self-report adherence measure
Bender et al., 2010[2] NA	Yes	Yes	NA	Medium	Few baseline characteristics measured so difficult to evaluate the success of randomization; Recruitment occurred through ads in newspapers: the self-selection may have resultant in disproportionately large gains
Berg et al., 1997[3] NA	Yes	Yes	NA	Medium	Method NR or inadequately reported
Berger et al., 2005[4] NA	Unclear or NR	yes		Medium	The danger of social desirability bias may be high due to self-report persistence measure. It is also unclear whether the outcome assessors were blinded to the random status of the patients.
Bogner et al., 2010[6] NA	Unclear or NR	Yes	NA	Low	The study uses ITT analysis and clearly describes potential outcomes, their measures, and rationale for using these measures. The main concern is that several key procedures are not clearly described or reported, such as how randomization was conducted and whether outcome assessors were properly blinded to participants' treatment assignments. On the other hand, blinding participants or providers in this study was probably not feasible because of the nature of the intervention and its clear distinction from the usual care treatment. This study has a low risk of bias because the strengths of the study design, such as the 0% attrition rate and use of the MEMS adherence measure, seem to outweigh the uncertainties.

Author, Year Trial name	Harms assessed using valid and reliable measures, implemented consistently across all study participants?	Potential outcomes pre-specified by researchers? Are all pre-specified outcomes reported?	[For observational studies only] Important confounding and modifying variables taken into account in the design and/or analysis?	Risk of bias	Comments
Bogner et al., 2008[5] NA	NA	Yes	NA	Medium	No information on randomization and allocation concealment; unclear whether outcome assessors were blinded
Bosworth et al., 2005[7] V-STITCH	NA	Yes	NA	Medium	Unclear if outcome assessors blinded; baseline adherence not stratified by intervention vs. control group; self-report adherence measures
Bosworth et al., 2008[8] TCYB Bosworth et al., 2007[9] TCYB Methods paper	NA	Yes	NA	Medium	This study only reports preliminary 6 month results; details of study that would help with quality assessment were not been reported (i.e., randomization, blinding, etc.)
Brown et al., 2008[10]	NA	No	N/A	High	randomization, intervention, and I/E criteira varied by site (e.g., one site randomized w/n disease severity strata); med adherence measure not pre-defined
Capoccia et al., 2004[11] NA	NA	Yes	NA	Medium	Risk of bias: medium: the clinical pharmacist not only did the intervention but was involved in screening patients for eligibility, and measure of adherence is self-reported; unclear to what extent the intervention is standardized and whether protocol was maintained; possible Hawthorne effect
Carter et al., 2008[12] NA	Unclear or NR	Yes	NA	High	This study received a high risk of bias rating because the investigators suggest their attempts to keep physicians and enrolled patients blinded did not work. Physicians were able to refer patients to the study, which introduces risk of nondifferential selection bias. It also was not clear if the investigators used allocation concealment. Still, there were several strengths, including ITT analysis, good randomization, blinding of outcome assessors, low attrition, and use of a good adherence measure.

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Carter et al., 2009[13] NA	Unclear or NR	Yes	NA	Medium	Medication adherence was measured with a self-report questionnaire, which may introduce information bias. It is unclear whether allocation concealment was used or whether blinding was used at all.
Chernew et al., 2008[14] NA	NA	Yes	Partial (some variables were taken in to account)	Medium	There were differences between the intervention and comparison group. The investigators did little to control for these differences. The possibility of unmeasured differences also cannot be ruled out. In addition, the sample varied over time and this is not described in sufficient detail to permit an assessment of potential impact on findings.
Choudhry et al., 2010[15] NA	NA	Yes	Partial (some variables were taken in to account)	Medium	The investigators were unable to account for other interventions/exposures that could have affected the results. They also did not provide a rationale for how they set their medication adherence threshold of 80%, so this could lead to measurement bias. A lot of important information needed for quality assessment was not reported, such as attrition and whether ITT analysis was used.
Choudhry et al., 2011[16] MI FREEE	Yes	Yes		Low	
Esposito et al., 1995[17] NA	NA	yes		high	Very small sample and study arms differ in several characteristics. There were no statistical analyses of results.

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Fortney et al., 2007[18] TEAM (Telemedicine Enhanced Antidepressant Management)	NA	Yes	NA	High	Medium / high - patient characteristics are similar; no information on characteristics of the clinics except that 5 clinics had on-site mental health providers (i.e. social workers); unclear how resources and intensity of interactions with healthcare personnel aside from PCPs affected results; telemedicine appears to have been used at low rate (specific rate not reported); also study only conducted in clinics that had telemedicine equipment-- possible that these clinics are not generalizable to other clinics. Increased risk of bias from self-reporting of adherence info. Finally, p-values not reported with unadjusted estimates; they are provided with adjusted estimates, but unclear what covariates were included in the model. Also, not sure that this is truly an ITT analysis b/c adherence analysis only included subsample of patients with an active antidepressant prescription, and not reporting antidepressant discontinuation as a result of PCP instruction. col S: cut-off determined not by clinical evidence; authors cite comparability to other studies as rationale for cutoff
Friedman et al., 1996[19] NA	NA	Yes	NA	Medium	Both groups started out with a very high adherence rate; only data from those who completed study were used for analyses; article did not report the average number of calls made by the intervention group.
Fulmer et al., 1999[20] NA	NA	yes		Medium	SF-36 and MLHF may have been affected by social desirability bias in the intervention groups more than the control as the article implies that the daily reminders were administered by the same RA who collected follow-up data

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Grant et al., 2003[21] NA	NA	Yes	NA	Medium	Use of self-report by the interventionist as adherence measure and other lack of blinding and high attrition before intervention administers make risk greater than LOW but not high b/c randomization appears to have been done well and most attrition occurred same in both arms and was before intervention
Gould et al., 2011[92]	NA	Yes	N/A	High	Baseline characteristics not reported at all; differential attrition apparent- much lower drop-out rate in usual care groups than both intervention groups; method of randomization could be subverted easily and concealment broken easily; non-ITT analysis.
Guthrie et al., 2001[22] First Myocardial Infarction (MI) Risk Reduction Program	NA	Yes	NA	Medium	Very high attrition; medication adherence measure is not a validated measure; many quality measures unclear/NR
Hoffman et al., 2003[23] NA	NA	Yes	NA	Low	Comments: Zip codes of physicians were randomized, and then alternatingly assigned to each arm; No reporting of attrition but ITT analysis conducted.
Hunkeler, et al., 2000[24]	Yes	Yes	NA	High	Authors changed randomization scheme midway through the project to include a third active intervention group; results combined both active intervention groups and compared against usual care. It is unclear whether the absence of difference between usual care and active intervention can be explained by effects in opposite directions for the two embedded interventions arms within the active comparator.

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Hunt et al., 2008[25] NA	NA	Yes	NA	Medium	There was high attrition in both groups, no ITT analysis, adherence thresholds not described (e.g. what is "high adherence"?) however randomization methods were good, and the study showed no difference between groups therefore this study was given a medium risk of bias instead of a high risk of bias.
Janson et al., 2003[26] NA	NA	Yes	NA	Medium	Methods NR in detail; adherence was measured primarily through diary but also collected with medication monitors; in case of discrepancy between diary and monitor, used monitor data; unclear why didn't exclusively use monitor data and extent to which monitor and self-report were different
Janson et al., 2009[28] NA	NA	Yes	NA	Low	Only difference is in peak flow and Latino ethnicity—but essentially groups were similar; baseline characteristics of intervention and control clinicians not reported. Note that results reported in the abstract somewhat misleading in that they don't focus on comparison of intervention and control arms across follow-up period despite the fact that the goal of the intervention was to increase long-term adherence.
Janson et al., 2010[27] NA	NA	Yes	NA	High	Patients were blinded to treatment group by providers were not; no info. Given describing provider characteristics or info about their inclusion. Clinic does NOT use electronic medical records; clinicians are the unit of randomization (and their panel of patients considered in either G1 or G2), but patients are often seen by different clinicians for follow-up visits

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Johnson et al., 2006[30] NR	NA	Yes	NA	Medium	Attrition is very high and doesn't appear this was an ITT analysis, study does not stratify n analyzed by intervention vs. control group; whether there are differences in baseline characteristics is also unclear, so much is unknown about quality metrics, difficult to assess if medium vs. high risk of bias
Johnson et al., 2006[29] NR	NA	Yes	NA	Medium	Difficult to tell since many elements not reported
Johnston et al., 2000[31] NA	Unclear or NR	Yes	NA	High	Multiple potential sources of bias, unclear how randomized, non-blinded, outcome measure for adherence unclear.
Katon et al., 1996[33] NA	NA	Yes	NA	Medium	Unclear how many patients from each group were analyzed for some of the health outcomes. The adherence outcomes, 50% or more reduction in depressive symptoms, and patient satisfaction were done by ITT analysis; other outcomes used 141 patients who completed 2 follow up, but the study does not report information about how many in each group were included in these analyses.
Katon et al., 2001[36] NA Ludman et al., 2003[37] NA Van Korff et al., 2003[38] NA	NA	Yes	NA	Medium	Allocation concealment unclear; although rate of attrition for medication adherence outcome is low overall (differential rate unspecified), differential rates of attrition between arms for health outcomes of 6.2% in the intervention arm and 12.5% in the control arm

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Katon et al., 2004[39] Pathways	NA	Yes	NA	High	Intervention based on IMPACT intervention (which is referenced) but nature of contact between nurses and patients not well described. Approx 20% of participants from each group dropped out; unclear if characteristics of participants who dropped out differed by group. The intervention itself includes prescriptions for AD, but only for some patients, so the outcome of adherence is endogenous to the intervention. In this context, it is impossible to attribute the change in refills to improvement in adherence; the change could just be the result of initiation of the new drug prescribed. The measure does not take into account number of prescriptions or number of medications.
Katon et al., 1995[32] NA	NA	Yes	NA	Medium	Results for medication adherence are not presented for the entire sample; they are presented for major and minor depression, the strata within which the strata were randomized. The strata, however, were constructed based on SCL depression scores, but the analysis was presented based on IDS scores that became available after randomization. The difference between randomization groups and analysis groups is unclear.
Katon et al., 1999[34] NA Katon et al., 2002[35] NA	NA	Yes	NA	Medium	70% of participants completed all follow-up assessments; ITT analysis conducted but only the 82% who were enrolled in HMO for at least 3 of 5 6-month periods and were included in adherence & cost analyses; Adequate dosage guidelines justified, but thresholds for medication adherence not supported
Laramee et al., 2003[40] NA	NA	Yes	NA	High	Attrition is extremely high and uncertain how many participants were analyzed for med adherence outcomes; given problems with randomization, would consider high.

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Lee et al., 2006[41] FAME	NA	Yes	NA	Medium	Different measurement method and frequency between intervention and control group for 14 month outcomes, no blinding
Lin et al., 2006[42] NA	Unclear or NR	Yes	NA	Medium	The adherence measure in this study, computerized pharmacy refill records, was vulnerable to bias. It only measured medication refills, not actual usage by participants. As a result, it may have overestimated or even underestimate adherence rates. Data for diabetes self-management behaviors may have been affected by information bias, since they were based on self-report.
Maciejewski et al., 2010[43] NA	NA	Yes	Partial (some variables were taken in to account)	Medium	Several important factors not considered in analysis controlling for covariates, including ethnicity/race and income. The study used several measures to reduce the risk of bias due to confounding, in particular propensity score matching.
Mann et al., 2010[44] The Statin Choice	NA	Yes	NA	Medium	The combination of risk of bias for the outcome measure by arm and lack of any reporting of attrition or ITT analysis - CW: There is not enough information to determine the answers for many of the quality questions, so in the absence of information to say for sure, this would probably have a medium risk and not a high risk of bias.
Martin et al., 2011[45] HARP	NA	Yes	N/A	High	very high attrition without reports on n analyzed from each group; non-ITT analysis
Montori et al., 2011[46] NA	NA	Yes		Low	

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Mundt et al., 2001[47] NA	NA	Yes	NA	High	There was a high attrition rate in both groups (73.8% of intervention group completed all three follow up calls, and 66.9% of control group completed all three calls); the medication compliance analysis excluded 75 out of 246 (30%) patients (33 intervention and 42 control patients), the text explains that patients were excluded because they had prescription refill records in excess of 15 days (25), no prescription records (3), or a single prescription fill (26). These post-hoc exclusions (for reasons of the adequacy of prescription fill data) could result in unaccounted-for differences between the originally randomized arms. No sensitivity analysis was reported to indicate how the excluded group compared to the subgroup retained in the analysis.
Murray et al., 2007[48] NA	Yes	Yes	NA	Low	NA
Nietert et al., 2009[49] NA	NA	No	NA	Medium	The randomization method was effective, and the sample size seemed adequate. On the other hand, 2 of the 9 study locations had no refill data for the first 5 months of the study, and gender information was missing for the study sample. Also, race, education, and income data were all based on population-level data in each patient's zip code of residence, rather than each individual's information. Assuming that this group-level data also applies to the sample size leaves room for bias. Finally, it was unclear whether the adherence measure in this study, time-to-refill, is valid and reliable.
Odegard et al., 2005[50] NA	NA	Yes	NA	High	Not randomized by clinic, patient level randomization not described, high attrition in control group (20%) (Intervention group was 10 %); Not just greater attrition in control group, but many fewer were randomized to control group.

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Okeke et al., 2009[51] NA	Unclear or NR	Yes		Medium	It is unclear whether treatment arm was concealed from medical provider or from study staff assessing outcomes.
Park et al., 1996[52] NA	yes	yes		high	The pharmacists delivering the intervention were responsible for recruiting, consenting, randomizing, intervening, and collecting data on all patients. Providers were not blinded. Sample size was small and far more control patients than study patients had controlled BP.
Pearce et al., 2008[53] Cardiovascular Risk Education and Social Support (CaRESS) Trial	Unclear or NR	Yes	NA	Medium	There is a medium risk of bias for several reasons. There is potential information bias because medication adherence was measured using a self-report questionnaire instead of an objective measure like MEMS. Confounding by health insurance status is unlikely but possible, since there were significant between-group differences in this variable at baseline. Also, the power of the study to avoid type II errors was limited because of insufficient recruiting.
Planas et al., 2009[54] NR	NA	Yes	NA	High	Small sample size (40 for adherence outcomes), high attrition; number of medications at baseline not accounted for; baseline characteristics appear to differ for ethnicity and BMI
Powell et al., 1995[55] NA	NA	Yes	NA	Medium	The investigators did not take baseline disease co-morbidities into account (potential confounder), and their method of deducing their subjects' disease states based on the drug prescribed seems prone to bias, as well. For example, what if a large group of patients received their medications for off-label usage? Too little information is provided about blinding and allocation concealment, so it wasn't possible to rate the study on these traits.
Powers et al., 2011[56] NA	NA	Yes	N/A	Medium	blinding and randomization methods unclear; using self-reported measure for adherence

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Pyne et al., 2011[57] HIV Translating Initiatives for Depression Into Effective Solutions (HITIDES)	NA	Yes	NA	Medium	Low rates of attrition for the overall intervention study, but low response rates for measuring outcomes. Risk of Hawthorne effect; validity of outcome assessment unlikely to vary by study group
Rich et al., 1996[58] NA	NA	Yes	NA	Medium	A few significant/borderline differences between groups: 1) age (older in treatment group) p=0.029 2) heart rate (higher in treatment) p=0.004 3) serum cholesterol (higher in treatment) p = 0.052 Analysis did not control for differences
Rickles et al., 2005[59] NA	NA	Yes	NA	Medium	Col H: baseline characteristics similar except for intervention group had more people with past history of psychiatric meds; not adjusted for in the analysis col p: main analysis is not intent to treat; however, noted that with ITT analysis, no sign. difference across study arms on adherence measures at 6 mos. Risk of bias: Medium -- no blinding in the study; numbers were small and ITT analysis showed no effect; also authors chose to use 1-sided statistical tests; if used 2-sided test, unclear if non-ITT results would still be statistically significant; unclear if the much higher proportion of previous psychiatric meds in the intervention arm resulted in a group that was more resistant to the intervention, which may explain the lack of effect of the intervention
Rodin et al., 2009[60] NA	NA	Unclear or NR	No (Not accounted for or not identified)	High	The investigators did not control for any potential confounding variables in their analyses. This, compounded by the differences at baseline between the intervention and control groups, resulted in the high risk of bias rating.

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Ross et al., 2004[61] NR	NA	Yes	NA	Medium	Providers did not know which patients enrolled in study unless they received communication from patient using SPPARO so no protocol to keep providers blinded; difference in 12-month attrition between groups ~10%; small n
Rudd et al., 2004[62] NA	NA	Yes	NA	Medium	Randomization method unclear, baseline adherence not reported, unclear if ITT analysis
Rudd et al., 2009[63] NA	Unclear or NR	Yes		Low	Adherence was measured only through self-report.
Ruskin et al., 2004[64] NA	NA	Yes	NA	High	Possible detection bias from failure to validate adherence threshold & reduced power to detect statistical differences in adherence due to overall attrition. Possible risk of contamination because same providers delivered treatment in both intervention groups (although treatment goals were identical between groups). Also, authors raise concern that adjustment for medical comorbidities was insufficient. The study had 12 post-randomization exclusions from 131 randomized, an additional 46 patients dropped out of the adherence analysis, leaving 56% of the original randomized sample. The adherence analysis is not based on intention-to-treat. The 70% cutoff for the dichotomous outcome of adherence is not supported by evidence. There was a possible Hawthorne effect.
Schaffer et al., 2004[65] NA	NA	No	NA	Medium	Inclusion and exclusion criteria not described; small sample size likely limited ability to test differences across groups
Schectman et al., 1994[66] NA	NA	Yes	NA	Medium	No reports on method of randomization; very high attrition >20% in niacin >30% in BAS and non-ITT analysis done (only subjects maintained on drug for 2 months analyzed- see Table 3); follow-up time to outcomes extremely short- only 2 months

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Schneider et al., 2008[67] NA	Unclear or NR	Yes		Low	
Schnipper et al., 2006[68] NA	Unclear or NR	yes		Low	
Shu et al., 2009[69] NA	Unclear or NR	Yes		High	This study was a post-hoc analysis of an RCT with different outcomes from adherence. Additional details on study quality may be reported in another article: Solomon DH, Polinski JM, Stedman M, et al. Improving care of patients at-risk for osteoporosis: a randomized controlled trial. JGIM 2007; 22(3):362-367.
Simon et al., 2006[70] NA	NA	Yes	NA	Medium	Risk of bias: Medium: assessed success of baseline randomization using few characteristics; characteristics of psychiatrists unknown; The adherence measure is weak b/c prescription refills could be missing for 1/2 of study time (3 months) and person could still be considered perfectly adherent if adherent for another 3 months Other comments: col H: few baseline characteristics recorded; usual care group was sign. older than intervention groups: the adherence measure is filled prescriptions for at least 90 days of continuous antidepressant treatment at a minimally adequate dose - specific doses for specific meds - doses appear to be derived clinically but not referenced as mentioned above, could be nonadherent for half of follow-up time but still considered adherent.
Sledge et al., 2006[71] NA	Unclear or NR	No		Medium	Adherence was not a main aim of the study and was not reported in the results.
Smith et al., 2008[72] NR	NA	Yes	NA	Medium	One site was randomized by patient instead of practice; contamination could have underestimated effect of intervention

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Solomon et al., 1998[73] NA Gourley et al., 1998[74] NA	NA	Unclear or NR	NA	Medium	Difficult to fully assess quality given many items unknown; attrition unclear so can't tell if ITT analysis done, lack of masking of participants and outcome assessors, etc.
Stacy et al., 2009[75] NA	NA	Yes	NA	Medium	Non-ITT analysis, not sure if randomization was adequate; certain exclusions made after randomization occurred creating a population that is already fairly adherent and motivated to take their statins
Stuart et al., 2003[76] NA	NA	No	NA	High	Methods, data, results inadequately reported. High attrition rates (50%) in at least one arm, other attrition rates NR, no results reported in text, unclear if results addressed high attrition rate.
Taylor et al., 2003[77] NA	NA	yes		Medium	There are many aspects of the randomization and data collection procedures that are not reported, and the compliance outcome was assessed by self-report.
Vivian et al., 2002[78] NA	NA	Yes	NA	Medium	Compliance measured monthly in intervention group; only measured at baseline and at 6 months for control group; small n
Waalen et al., 2009[79] NA	Unclear or NR	Yes		Medium	It is unclear whether treatment arm was concealed from study staff assessing outcomes. The authors also report an independent HMO-wide program to improve osteoporosis treatment which would have impacted only the control arm.
Wakefield et al., 2008[80] NA	Unclear or NR	Yes	NA	High	High differential attrition at 180 days in videotelephone group, baseline differences between control and intervention groups in changes to medications at discharge and understanding regimen; approximately 2.6 video calls (out of 14) were transitioned to telephone calls due to technical errors; single question, non-validated assessment of adherence.

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Wakefield et al., 2009[81] NA	Unclear or NR	Yes	NA	High	High differential attrition at 180 days in videotelephone group, baseline differences between control and intervention groups in changes to medications at discharge and understanding regimen; approximately 2.6 video calls (out of 14) were transitioned to telephone calls due to technical errors; single question, non-validated assessment of adherence.
Wakefield et al., 2011[82] NA	NA	Yes	N/A	Medium	measure of medication adherence is weak and data not reported
Weinberger et al., 2002[83] NA	NA	Yes	NA	Low	Information on allocation concealment and blinding concealment not reported; study used only self-report measures of adherence
Weymiller et al., 2007[84] Statin Choice Randomized Trial Jones et al., 2009[85] Statin Choice Randomized Trial	Unclear or NR	Yes	NA	Medium	In the Weymiller and Jones articles, the investigators did a commendable job of protecting the internal validity of their study data by computerizing randomization and provider allocation, blinding participants and outcome assessor to group assignments, and ITT analysis. Unfortunately, baseline adherence rates were not calculated, and the only measure of adherence was a single self-report "Yes/No" item, which could introduce information bias.
Williams et al., 2004[86] IMPACT (Improving Mood–Promoting Access to Collaborative Treatment)	NA	Yes	NA	High	Ceiling effect on baseline adherence measure makes it impossible to assess whether lack of difference at follow-up is an artifact of measurement of adherence.

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Williams et al., 2010[87] NA	NA	Yes	NA	Low	Col J: providers were the target of the intervention - they were not blinded; unclear if patients were blinded. Physicians were given access to data, but most physicians did not use the data. Like an effectiveness trial to see whether intervention would be taken up by physicians.
Wilson et al., 2010[88] Better Outcomes of Asthma Treatment (BOAT); note that there is online supplemental material for methods and timeline	Yes	Yes	NA	Medium	No ITT analysis; included participants with complete data for the entire year of analysis; Computer-based adaptive randomization algorithm used to ensure concealment and better-than-chance balance among the three groups for baseline characteristics; inclusion criteria somewhat vaguely described
Wolever et al., 2010[89] NA	NA	Yes	NA	Medium	
Zeng et al., 2010[90] NA	NA	Unclear or NR	Partial (some variables were taken in to account)	High	Analyses used different numbers of control group patients (e.g. PDC included 710 total (71 cases, 639 controls). The intervention group was limited to patients at one clinic. Not clear why that clinic was selected.
Zhang et al., 2010[91] NA	NA	Unclear or NR	Yes	Medium	Comparison group differed from intervention groups. Propensity scores may not adequately adjust for all potential confounders.

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Appendix F. Adherence and Clinical Outcome Scales Commonly Used in Medication Adherence Studies

General Health Measures

Abbreviated Name	Complete Name of Measure or Instrument	Range or mean of Scores	Improvement Denoted by
ACT	Asthma Control Test	0-25.	Increase
ACQ	Asthma Control Questionnaire	Total score is mean of scores for all 7 items.	Decrease
AQLQ	Asthma Quality of Life Questionnaire	0-4. A score change of 0.5 points is considered to be clinically important.	Increase
ATAQ	Asthma Therapy Assessment Questionnaire	0-4	Decrease
CES-D	Center for Epidemiologic Studies – Depression Scale	0-60	Decrease
DSM-III/IV	Diagnostic and Symptom Manual III/IV	N/A	N/A
N/A	Hypertension/Lipid Form 5.1 (developed by The Health Outcomes Institute)		
IDS	Inventory of Depressive Symptomatology	0-84	Decrease
MLHF	Minnesota Living with Heart Failure	NR	Increase
SCL-20	Symptom Checklist with 20 items	NR	Decrease
SF-36	Medical Outcomes Study Short Form 36 Health Survey	0-100	Increase
N/A	Sheehan Disability Scale	0-10	Decrease

Medication Adherence Measures

Abbreviated Name	Complete Name of Measure or Instrument	Range or mean of Scores	Improvement Denoted by
HEDIS	Healthcare Effectiveness Data and Information Set guidelines for measuring adherence based on pharmacy refill data	N/A	N/A
MPR	Medication possession ratio (i.e, number of eligible days in the yearly quarter the person was in possession of the medication divided by the number of days in the quarter)	0-1.0	Increase
MEMS	Medication event monitoring systems	N/A	Increase
N/A	Morisky 8-item adherence scale	0-8	Decrease
N/A	Proportion of days covered (i.e., estimated number of days of medication available to each patient)	Continuous	Increase
N/A	Time-to-refill	Measured in days	Decrease

Appendix G. Patient, Provider, and Policy Interventions: Summary Evidence Tables

Table G1. Diabetes: biomarker hemoglobin A1C (HbA1C)

Author, Year N in Each Group	Outcome	Results
Bogner et al., 2010[1] 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 G2. Hyperlipidemia: biomarkers

Author, Year N in Each Group	Outcome	Results
Lee et al., 2006[2]		
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 G3. Hyperlipidemia: patient satisfaction

Author, Year N in Each Group	Outcome	Results
Weymiller et al., 2007[3] Jones et al., 2009[4] 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 G3. 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 G4. Hypertension: morbidity

Author, Year N in Each Group	Outcome	Results
Bogner et al. 2007[5] 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[6] 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[2] G1: 73 G2: 62	Among patients with 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 hypertension: difference between systolic blood pressure at 2 months and 14 months (6-month cohort + 6-month RCT outcome)	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 hypertension: diastolic blood pressure at 14 months (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 hypertension: difference between systolic blood pressure at 2 months and 14 months (6-month cohort + 6-month RCT outcome)	G1: -2.5 mm Hg (95% CI, -4.9, -0.2) G2: -1.2 mm Hg (95% CI, -3.7, 1.2) p: 0.39
Rudd, et al., 2004[7] G1: 74 G2: 76	Change in systolic 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: 74 G2: 76	Change in diastolic blood pressure between baseline and 6 months Measured by blinded study personnel	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

Table G4. Hypertension: morbidity (continued)

Author, Year N in Each Group	Outcome	Results
Schneider et al., 2008[8] 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 G4. 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[9,10] 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 months) 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 G5. Hypertension: quality of life

Author, Year N in Each Group	Outcome	Results
Solomon et al., 1998[9,10]	Hypertension group:	Visit 1 (baseline)
G1: NR	Proportion of participants	G1: 22 (34.0%)
G2: NR	reporting problems with sexual	G2: 19 (26.0%)
	functioning during previous 4	95% CI, NR
	weeks	p: NR
	- From Lipid Form 5.1	Visit 5 (between 4 and 6 months)
	developed by the Health	G1: 8 (2.5%)
	Outcomes Institute	G2: 8 (25.0%)
	Self-report	95% CI, NR
		p: NR
G1: NR	Hypertension group:	G1 (baseline): 22 (34.0%)
G2: NR	Participants reporting	G1 (between 4 and 6 months): 8 (2.5%)
	problems with sexual	95% CI, NR
	functioning during previous 4	p: 0.003
	weeks, within-group	G2 (baseline): 19 (26.0%)
	comparison	G2 (between 4 and 6 months): 8 (25.0%)
	- From Lipid Form 5.1	95% CI, NR
	developed by the Health	p: NR
	Outcomes Institute	
	Self-report	
G1: NR	Hypertension group: "Feeling	Visit 1 (baseline)
G2: NR	dizzy upon standing up," mean	G1: 1.7 (1.1 SD)
	score on Likert scale of 1	G2: 2.0 (1.1 SD)
	(never) to 5 (very often)	95% CI, NR
	- From Lipid Form 5.1	p: NR
	developed by the Health	Visit 5 (between 4 and 6 months)
	Outcomes Institute	G1: 1.4 (0.8 SD)
	Self-report	G2:1.4 (0.8 SD)
		95% CI, NR
		p: NR
G1: NR	Hypertension group:	Visit 1 (baseline)
G2: NR	“Headaches more than usual,”	G1: 1.5 (1.0)
	mean score on a Likert scale	G2: 1.6 (1.2)
	of 1 (never) to 5 (very often)	95% CI, NR
	- From Lipid Form 5.1	p: NR
	developed by the Health	Visit 5 (between 4 and 6 months)
	Outcomes Institute	G1: 1.2 (0.8)
	Self-report	G2:1.2 (0.8)
		95% CI, NR
		p: NR

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

Table G6. Hypertension: patient satisfaction

Author, Year N in Each Group	Outcome	Results: Mean (SD)
Solomon et al., 1998[9,10] 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 G7. Hypertension: health care utilization

Author, Year N in Each Group	Outcome	Results
Schneider et al., 2008[8] 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[9,10] G1: 63 G2: 61	Hypertension group: Mean number of Emergency Room visits in 4 weeks prior - at 4-6 month 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 month 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 month 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 G8. Heart failure: quality of life

Author, Year N in Each Group	Outcome	Results
Fulmer et al., 1999[11] 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 follow-up (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[12] 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[13] 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 G8. 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 G8. 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 G9. Heart failure: patient satisfaction

Author, Year N in Each Group	Outcome	Results
Murray et al., 2007[12] 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[13] 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 G9. 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 G10. Heart failure: healthcare utilization including emergency department visits, hospitalizations, and clinic visits

Author, Year N in Each Group	Outcome	Results
Murray et al., 2007[12] 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 G10. 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[14] 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[13] 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

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

Table G11. Heart failure: cost

Author, Year N in Each Group	Outcome	Results
Murray et al., 2007[12] 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 G12. Heart failure: mortality

Author, Year N in Each Group	Outcome	Results
Ross et al., 2004[13] G1: NR G2: NR	Deaths (%)	**12 months:** G1: 6 (11%) G2: 6 (11%) 95% CI, NR p=1.00

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

Table G13. 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 [15] 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 [16] 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 [17] 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=0.457
	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 G14. Reactive airway diseases: morbidity

Author, Year N in Each Group	Outcome Source/Method	Results
Bender et al., 2010[18] 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[19] 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[15] 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[16] 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 G14. 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 [20] 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 G14. 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 [17] 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 G15. Reactive airway diseases: quality of life

Author, Year N in Each Group	Outcome Source/Method	Results
Bender et al., 2010 [18] 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 [15] 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 [16] 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 [20] 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 [17] 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 G16. Asthma: health care utilization

Author, Year N in Each Group	Outcome Source/Method	Results
Wilson et al., 2010 [17] G1: 204 G2: 204 G3: 204	Number of asthma-related visits per year Electronic medical records	Means at 1 year post-randomization: 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 G17. Depression: morbidity

Author, Year N in Each Group	Outcome Source	Results
Bogner et al., 2007[5] 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
Bogner et al., 2010[1] 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[21] 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 Symptomatology (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 G17. 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[22] 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;[23] Katon et al. 2002[24] 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: 0.88 (0.52) G2: 1.23 (0.62) 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 G17. 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;[25] Ludman et al., 2003;[26] Von Korff et al., 2003[27] 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 G17. 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 G17. 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 G17. 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 G18. Depression: patient satisfaction

Author, Year N in Each Group	Outcome Source	Results
Katon et al., 1995[21] 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[22] 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 G19. Depression: health care utilization

Author, Year N in Each Group	Outcome Source	Results
Katon et al.,1995[21] 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[22] 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 G19. Depression: health care utilization (continued)

Author, Year N in Each Group	Outcome Source	Results
Katon et al., 1999;[23] Katon et al., 2002[24] 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 non-study 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 non-study 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 G20. Depression: costs

Author, Year N in Each Group	Outcome Source	Results
Katon et al., 1999;[23] Katon et al., 2002[24] 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
	Non-depression 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 G21. Depression: quality of care

Author, Year N in Each Group	Outcome	Results
Katon et al., 1995[21] 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[22] 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;[23] Katon et al., 2002[24] 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 G22.Glaucoma: morbidity

Author, Year N in Each Group	Outcome	Results
Okeke et al., 2009[28] 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 G23. Musculoskeletal diseases: patient satisfaction

Author, Year N in Each Group	Outcome	Results
Waalen et al., 2009[29] G1: 68 G2: 58	Patient satisfaction with care assessed by 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: 58 (85.3) G2: 52 (89.7) 95% CI, NR Some of the time: G1: 4 (5.9) G2: 0 (0) 95% CI, NR A little/none of the time: G1: 6 (8.8) G2: 6 (10.3) Overall p: 0.17
Montori et al., 2011[30] G1: NR G2: NR	Mean satisfaction with knowledge transfer measured using 16-item decision conflict scale NR	Amount of information G1: 6.6 G2: 6.3 95% CI, NR p: 0.798 Clarity of information G1: 6 G2: 6 95% CI, NR p: 0.296 Helpfulness of information G1: 6 G2: 5.8 95% CI, NR p: 0.624 Would want other decisions G1: 6.1 G2: 5.8 95% CI, NR p: 0.248 Would recommend to others G1: 6.4 G2: 6.2 95% CI, NR p: 0.435

Abbreviation: G = group.

Table G24. Policy interventions: clinical outcomes

Author, Year N in Each Group	Outcome Source	Results
Choudhry et al., 2011[31] G1: 2845 G2: 3010	Death from cardiovascular causes (rate/100 person-years) Health claims records	G1: 1.7 G2: 2.0 HR (95% CI): 0.85 (0.60-1.21)
	Rate of first fatal or nonfatal vascular event or revascularization (rate/100 person-years) Health claims records	G1: 17.6 G2: 18.8 HR (95% CI): 0.93 (0.82-1.04)
	Rate of all fatal or nonfatal vascular events or revascularization Health claims records	G1: 21.5 G2: 23.3 HR (95% CI): 0.89 (0.80-0.99)
	Rate of first fatal or nonfatal vascular event Health claims records	G1: 11.0 G2: 12.8 HR (95% CI): 0.86 (0.74-0.99)

Abbreviations: G = group; N = number; NA = not applicable; CI = confidence interval; ACE Inhibitor = angiotensin-converting-enzyme inhibitor; ARBs = angiotensin-receptor blockers; HR = hazard ratio.

Table G25. Policy interventions: economic outcomes

Author, Year N in Each Group	Outcome Source	Results
Choudhry et al., 2011[31] G1: 2845 G2: 3010	Total insurer spending (US dollars) Health claims records	Mean (SD) G1: 64,726 (639,683) G2: 69,997 (617,650) Relative Spending (95% CI): 0.92 (0.55-1.56)
	Total patient spending (US dollars) Health claims records	G1: 1,282 (1,549) G2: 1,781 (2,263) Relative Spending (95% CI): 0.74 (0.68-0.80)
	Combined insurer and patient total spending (US dollars) Health claims records	G1: 66,008 (639,970) G2: 71,778 (618,055) Relative Spending (95% CI): 0.89 (0.50-1.56)

Abbreviations: G = group; N = number; NA = not applicable; CI = confidence interval; ACE Inhibitor = angiotensin-converting-enzyme inhibitor; ARBs = angiotensin-receptor blockers; HR = hazard ratio

Table G26. Harms: adverse events outcomes

Author, Year N Analyzed in Each Group	Adverse Event Outcome Source	Results
Carter et al., 2009[32] G1: 192 G2: 210	Mean total adverse event score Adverse event questionnaire with 47 items, developed for another study and administered by study nurses	Measured twice, once at baseline and once at 6-month followup 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[12] G1: 112 G2: 192	Number of patients who had an adverse drug event or medication error 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[33] Niacin: G1: 40 G2: 40 BAS: G1: 18 G2: 20	Percentage of patients reporting adverse events associated with medications at 2 months Self-report to clinic staff	2 months; measured at 2, 4, and 6 months; only 2-month results reported 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**.**

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