Evidence Report/Technology Assessment
Number 208

4. Medication Adherence Interventions: Comparative Effectiveness

Closing the Quality Gap: Revisiting the State of the Science

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]

Evidence-based Practice Program

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. 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.

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

The full report and this summary are available at www.effectivehealthcare.ahrq.gov/reports/final.cfm.

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Evidence-Based Practice

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.

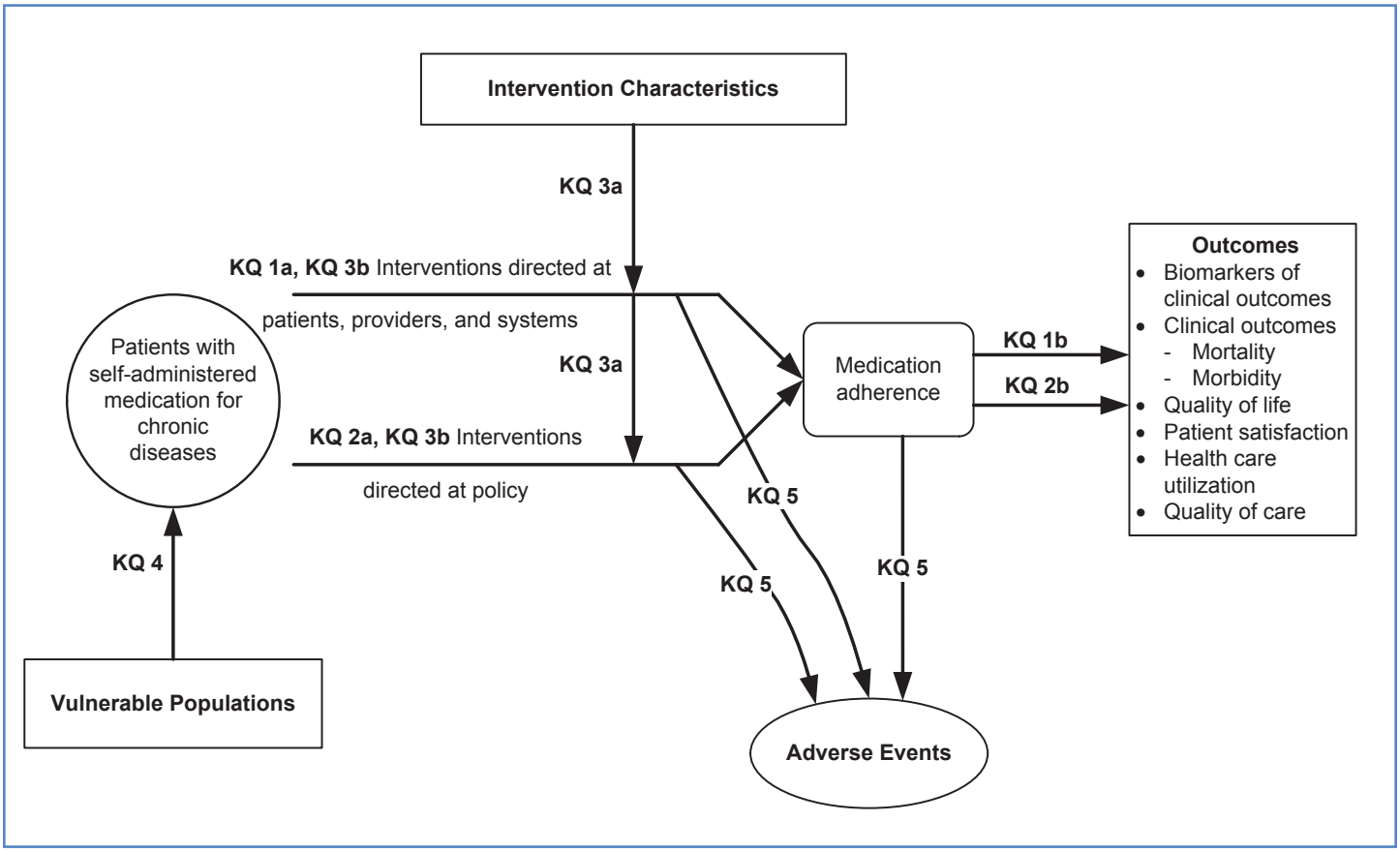
Literature Search and Review Strategy

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	

Table A. Inclusion and 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 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

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.

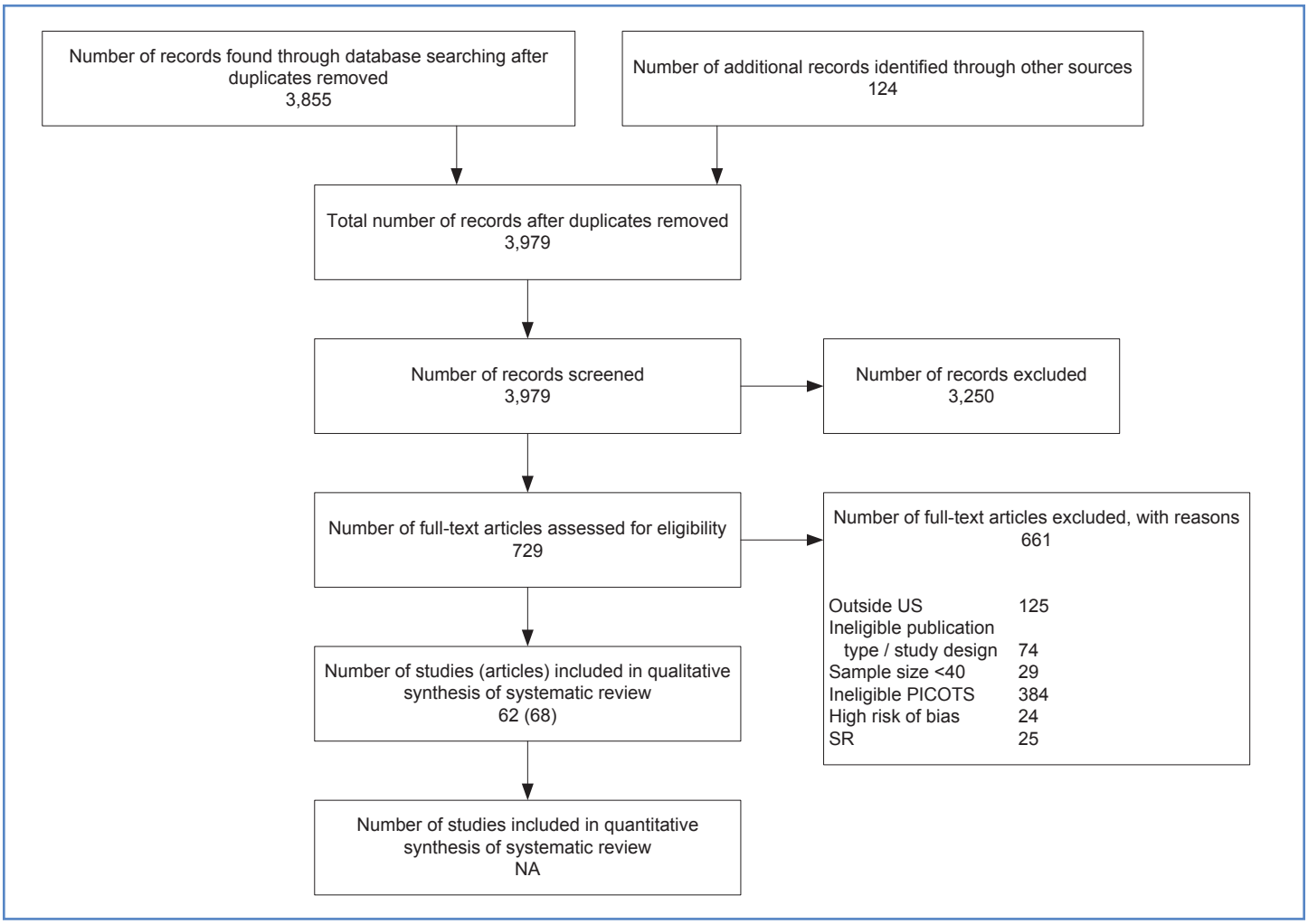
Results of Literature Searches

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).

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

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
Diabetes	Education with social support[36]	Insufficient for medication adherence	1; 199 (189)No stat sig difference	NA	NA
Diabetes	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
Hyperlipidemia	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
Hyperlipidemia	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
Hyperlipidemia	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
Hypertension	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)
Hypertension	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

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	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
				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	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

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	Education with social support[36]	Insufficient for medication adherence	1; 199 (199) No stat sig differences between groups at 12 months	NA	NA
Hypertension	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
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
Heart Failure	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

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	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
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 (3000 Varied measures and magnitude (inconsistent)
				Low SOE of no benefit for quality of life	4; 248 (245) Varied measures and magnitude (consistent)

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	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
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 geement[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

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
Depression	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
				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[84,85]	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[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

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 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
Musculoskeletal Diseases	Case management[90]	Insufficient for medication adherence	1; 127 (127) No stat sig difference	NA	NA
Musculoskeletal Diseases	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
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
Multiple or Unspecified Chronic Conditions	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	Glaucoma	MS	Musculo-skeletal Diseases	Multiple or Unspecified 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							

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

Type of Intervention	Diabetes	Hyper-lipidemia	Hyper-tension	Heart Failure	Myocardial Infarction	Asthma	Depression	Glaucoma	MS	Musculo-skeletal Diseases	Multiple or Unspecified Conditions
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.

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

Abbreviations: 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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