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Interventions to Improve Adherence to Self-administered Medications for Chronic Diseases in the United States

A Systematic Review

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Background: Suboptimum medication adherence is common in the United States and leads to serious negative health consequences but may respond to intervention.

Purpose: To assess the comparative effectiveness of patient, provider, systems, and policy interventions that aim to improve medication adherence for chronic health conditions in the United States.

Data Sources: Eligible peer-reviewed publications from MEDLINE and the Cochrane Library indexed through 4 June 2012 and additional studies from reference lists and technical experts.

Study Selection: Randomized, controlled trials of patient, provider, or systems interventions to improve adherence to long-term medications and nonrandomized studies of policy interventions to improve medication adherence.

Data Extraction: Two investigators independently selected, extracted data from, and rated the risk of bias of relevant studies.

Data Synthesis: The evidence was synthesized separately for each clinical condition; within each condition, the type of intervention was synthesized. Two reviewers graded the strength of evidence by using established criteria. From 4124 eligible abstracts, 62 trials of patient-, provider-, or systems-level interventions evaluated 18 types of interventions; another 4 observational studies and 1 trial of policy interventions evaluated the effect of reduced medication copayments or improved prescription drug coverage. Clinical conditions amenable to multiple approaches to improving adherence include hypertension, heart failure, depression, and asthma. Interventions that improve adherence across multiple clinical conditions include policy interventions to reduce copayments or improve prescription drug coverage, systems interventions to offer case management, and patient-level educational interventions with behavioral support.

Limitations: Studies were limited to adults with chronic conditions (excluding HIV, AIDS, severe mental illness, and substance abuse) in the United States. Clinical and methodological heterogeneity hindered quantitative data pooling.

Conclusion: Reduced out-of-pocket expenses, case management, and patient education with behavioral support all improved medication adherence for more than 1 condition. Evidence is limited on whether these approaches are broadly applicable or affect long-term medication adherence and health outcomes.

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Although many efficacious medical treatments exist, a recent Institute of Medicine report identified a gap between current treatment success rates and those believed to be achievable (1). This gap has been attributed partly to lack of patient adherence to recommended treatment (1, 2). Poor medication adherence is common (3, 4). Studies have consistently shown that 20% to 30% of medication prescriptions are never filled and that approximately 50% of medications for chronic disease are not taken as prescribed (5, 6).

This lack of adherence has dramatic effects on health (5, 7–16). In the United States, it is estimated to cause approximately 125 000 deaths, at least 10% of hospitalizations (5), and a substantial increase in morbidity and mortality (11, 12). Nonadherence has been estimated to cost the U.S. health care system between $100 billion and $289 billion annually (3, 5, 17–20).

This review is part of a larger initiative, Closing the Quality Gap: Revisiting the State of the Science, and builds on an earlier Agency for Healthcare Research and Quality (AHRQ) collection of publications, Closing the Quality Gap: A Critical Analysis of Quality Improvement Strategies (21). This new series focuses on selected settings, interventions, and clinical conditions for quality improvement. Our report addresses the comparative effectiveness of interventions to improve medication adherence.

Methods

The protocol and full review are available at http://effectivehealthcare.ahrq.gov. This article focuses on 2 of our key questions. First, among patients with chronic diseases with self-administered medication prescribed by a provider for secondary or tertiary prevention, what is the comparative effectiveness of interventions aimed at patients, providers, or systems in improving medication adherence? Is improved medication adherence associated with improved patient outcomes? Second, what is the comparative effectiveness of policy interventions for improving

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medication adherence? Is improved medication adherence associated with improved patient outcomes?

Study Eligibility

We assessed medication adherence effectiveness for studies conducted in outpatient primary and specialty care, as well as community-based and home-based settings (**Appendix Table 1**, available at www.annals.org). We excluded studies in institutional settings because medications are generally not self-administered there, interventions to improve antiretroviral adherence because comprehensive reviews of such interventions were only recently completed (22, 23), interventions for adherence to medications for patients with severe mental illness (schizophrenia, other psychoses, and bipolar disorder) and substance abuse because the complex cognitive features of adherence for such conditions require specific interventions that are not applicable to patients with other conditions, acute conditions because adherence for such disease differs from that for chronic illness (23), studies published before 1994 because of a large systematic review that included studies up to 1994 (24), and non–English-language and non-U.S. studies to ensure greater applicability of our findings to the unique health care setting of the United States. Other systematic reviews also note that adherence studies from non–U.S.-based health care systems are inherently different from those in the United States because of variations in the ways that patients procure, pay for, and monitor medications (25, 26).

Adherence is a complex multifactorial behavior that is influenced by social and economic factors (for example, age, race, sex, and socioeconomic status), patient-related factors (for example, knowledge, attitude, and beliefs), condition- and treatment-related factors (for example, severity of the symptoms and disease, complexity of the medical regimen, duration of treatment, and adverse effects), provider characteristics (for example, communication skills, training, and resources), and setting (for example, drug coverage, cost sharing of medications, and access to medication and clinical care) (27). Such factors interact to influence adherence behavior. For instance, the setting may influence patient and provider behavior through appointments that are too short to discuss adherence, fee structures that do not support reimbursement for patient counseling and education, poor continuity of care that disrupts the patient–provider relationship, and systems that impede information sharing between providers and pharmacists on prescription refills (27).

Hence, patient adherence behaviors in countries or settings without the systemic characteristics of the United States are markedly different. Residents of the United States have been found to be 2 to 3 times more likely to report cost-related nonadherence than Canadian residents (28, 29), even when the results were stratified by insurance status. Publicly or privately insured patients in the United States were more than twice as likely to report cost-related nonadherence than the reference group of patients who were seniors receiving social assistance in Ontario, Canada (29). Of note, in our review of 61 excluded non-U.S. studies, 7 were set in developing countries (30–36), 1 was a multicenter trial that included developing countries (37), and the remaining 53 were set in 15 advanced economies with universal coverage of various types (38–90). Of these, more than half were set in the United Kingdom (17 studies) (38–54) and Canada (10 studies) (55–64).

As suggested by Norris and colleagues (91), we conducted a preliminary assessment of the availability of evidence from randomized, controlled trials (RCTs) and the likelihood of selection bias and confounding from observational studies and accordingly focused on RCTs for patient, provider, and systems interventions. We expanded the scope to include observational studies for policy interventions because these studies allowed us to assess the effectiveness of policy innovations in practice settings that are not usually tested in trials.

Data Sources and Searches

To identify relevant articles, we conducted separate targeted literature searches for patient, provider, systems, and policy interventions by using MEDLINE, the Cochrane Library, and the Cochrane Central Register of Controlled Trials from 1994 through 4 June 2012. We reviewed our search strategy with a panel of technical experts and supplemented it as needed according to their recommendations. To avoid retrieval bias, we manually searched the reference lists of pertinent reviews to identify relevant citations that our searches missed.

Study Selection

Two trained researchers independently reviewed each title and abstract. All titles selected by at least 1 reviewer went on to full-text review by 2 independent reviewers. Reviewers resolved conflicts by discussion and consensus or consultation with a third reviewer as needed.

Data Extraction and Quality Assessment

For studies meeting the inclusion criteria, a trained reviewer abstracted data into structured evidence tables that were then reviewed by a second trained reviewer for completeness and accuracy.

Two independent reviewers assessed risk of bias for each study by using predefined criteria based on those developed by AHRQ (92) and specified in the RTI Item Bank (93). We resolved disagreements between reviewers by consulting a senior member of the team.

Data Analysis and Synthesis

To make the findings as clinically useful as possible, we analyzed results for each key question by both clinical condition and intervention type. We specified a priori the data to be collected for all outcomes except biomarkers and morbidity. On the basis of the recommendations of the technical expert panel, we elected to collect a comprehensive set of biomarkers and morbidity outcomes, rather than

judge which to collect in advance. We determined quantitative analysis to be inappropriate because of clinical or methodological heterogeneity, low numbers of similar studies, and insufficiency or in outcome reporting, so we synthesized data qualitatively. We grouped interventions into categories that reflected key intervention components.

We graded the strength of evidence for medication adherence, biomarkers (for example, systolic blood pressure and hemoglobin A_{1c}), morbidity (for example, depressive symptoms and asthma symptoms), mortality, and other health outcomes (94). These grades incorporate 4 key considerations when the strength of a stated effect is being evaluated: risk of bias (including study design and aggregate quality), consistency, directness, and precision (see **Appendix Table 2**, available at www.annals.org, for definitions of strength-of-evidence grades). We excluded studies with high risk of bias and found no variation in directness. As a result, consistency and precision were key drivers of the strength-of-evidence grades in this body of studies with medium and low risk of bias.

Role of the Funding Source

The AHRQ funded the systematic review. The key questions, protocol, and draft report were reviewed by the funder, the peer reviewers, the technical expert panel members, and the public. Approval from AHRQ was required before the manuscript could be submitted for publication, but the authors are solely responsible for its content and the decision to submit it for publication.

Results

First, we present the results from our literature search and a summary of the characteristics of our included studies. We then present our results for patient, provider, and systems interventions by clinical condition and intervention type. Supplement 1 and **Appendix Table 3** (available at www.annals.org) summarize our findings and give the strength-of-evidence grade for each intervention. Although we present our results separately by clinical condition and intervention type, the close correlation between these 2 factors requires that results synthesized by clinical condition specify intervention type. Similarly, results synthesized by intervention type specify clinical condition. Finally, we present results for policy interventions and summarize the findings in **Appendix Table 4** (available at www.annals.org). We generally highlight evidence of moderate or low strength.

Characteristics of Included Studies

Of the 4124 citations identified (**Appendix Figure**, available at www.annals.org), 758 published articles met inclusion criteria at the title and abstract review. Of these, 661 articles did not meet inclusion criteria on review of the full text. We excluded 24 additional articles with high risk of bias during data extraction. Of the 73 included articles (comprising 67 studies of low or medium risk of bias), 69 reported on RCTs and 4 reported on observational studies. Sixty-two provided data on patient, provider, and systems interventions (95–162). One trial and 4 observational studies provided information on policy interventions (163–167).

Most trials on patient, provider, or systems interventions provided information about 6 key characteristics: the targets, agents, methods, intensity, duration, and components of the interventions. The characteristics provided a framework by which we could describe the interventions. For example, for the targets, slightly more than 50% of the interventions were aimed at various combinations of multiple targets, whereas nearly 40% targeted only patients. Similarly, for delivery, a pharmacist, physician, or nurse delivered approximately 50% of interventions. About half of interventions involved at least some face-to-face delivery of the program. Supplement 2 (available at www.annals.org) presents information about each study's intervention, including its description, type, dose, and method of delivery.

Included trials of patient, policy, and systems interventions focus on hypertension (18 trials, 9691 patients), depression (13 trials, 11 445 patients), hyperlipidemia (9 trials, 19 228 patients), asthma (8 trials, 4423 patients), diabetes (6 trials, 1056 patients), heart failure (5 trials, 719 patients), multiple or unspecified chronic conditions (4 trials, 3403 patients), musculoskeletal diseases (4 trials, 2559 patients), myocardial infarction (1 trial, 907 patients), multiple sclerosis (1 trial, 435 patients), and glaucoma (1 trial, 66 patients). Of these, 7 studies examine more than 1 clinical condition. Fifteen studies (24%) were powered for adherence as a primary outcome (98, 107, 108, 124, 129, 131–133, 135, 139, 153–156, 159). Of note, we found no eligible studies for cancer, probably because we restricted this review to patient-administered medications in outpatient settings.

Included studies on policy interventions focus on cardiovascular disease (5 studies, >70 000 patients), diabetes (3 studies, approximately 20 000 patients), and respiratory conditions (1 study, number of patients not reported).

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

Overall, the evidence from 62 trials (68 articles) suggests that many pathways provide opportunities to improve medication adherence across clinical conditions. These approaches range from low-cost, low-intensity interventions, such as 1-time mailings, to intensive interventions, such as case management, care coordination, and collaborative care.

Despite evidence for promising approaches to improving medication adherence, we found relatively little evidence linking higher adherence to improvements in other outcomes, such as biomarkers, morbidity, mortality, quality of life, patient satisfaction, health care use, or costs. Of the 62 trials, 33 (53%) reported improvement in medica-

tion adherence. Of these 33 trials, 18 (29%) reported improvements in at least 1 health outcome, 8 (13%) reported no improvements in health outcomes, and 7 (11%) did not evaluate changes in health outcomes. The remaining 29 trials (47%) showed no improvement in medication adherence.

Findings Related to Clinical Conditions

Medication Adherence We found evidence supporting multiple effective interventions to improve medication adherence for the following conditions: hypertension (blister packaging, case management, education with behavioral support) (109–112, 116, 117, 122–124), heart failure (reminder calls; multicomponent, pharmacist-led interventions; education with behavioral support; case management) (127–130), depression (case management, collaborative care) (95, 111, 140–142, 144–147, 152), and asthma (self-management, shared decision making) (132–137). Not all interventions in these clinical areas, however, provided evidence of benefit. We graded the strength of evidence for some interventions as insufficient because of inconsistent or statistically nonsignificant results (98, 125, 126, 149, 150). In addition, we found evidence of no benefit of collaborative care for hypertension (97, 114, 115) or patient or provider access to patient adherence data for asthma (138, 139).

With respect to diabetes, hyperlipidemia, and musculoskeletal diseases, we found evidence of 1 effective intervention for each condition. These included care coordination and collaborative care for diabetes (95), education with behavioral support for hyperlipidemia (104–108), and virtual clinic for osteoporosis (157). All other intervention types studied for these clinical conditions had insufficient evidence of benefit, generally due to results that were inconsistent or not statistically significant (98, 99, 101–103, 109, 155, 156).

The least evidence of improvement in medication adherence, despite multiple trials testing 2 approaches, pertained to patients with multiple chronic conditions. Three trials testing 1 approach—pharmacist-led case management—resulted in no benefit for medication adherence (159–161). In addition, we judged evidence from another trial, which tested intensive interdisciplinary assessment followed by nurse-led case management, to be insufficient because the results were not statistically significant (162).

Other Health Outcomes We found the most consistent evidence for improved health outcomes attributable to better medication adherence for patients with hypertension, heart failure, depression, and asthma. For hypertension, both case management (96, 111, 112) and face-to-face education by pharmacists (109, 116, 117) led to enhanced adherence that decreased systolic and diastolic blood pressure. For heart failure, a pharmacist-led multicomponent adherence intervention reduced emergency department visits and improved patient satisfaction (129). Among patients with depression, case management reduced symptoms of depression (95, 111, 140–142), and collaborative care improved depression symptoms, patient satisfaction with medications, and quality of care (144–147). Finally, among patients with asthma, shared decision making improved symptoms, pulmonary function, health care use, and quality of life (137). We generally graded these interventions as beneficial, with low to moderate strength of evidence, depending on the specific type of intervention. We found very little evidence supporting a relationship between improved medication adherence and adverse events (data not shown).

Findings Related to Interventions

Of the 18 intervention approaches, 7 had been tested across different clinical conditions (**Appendix Table 3** and Supplement 2, available at www.annals.org): education; case management; reminders; pharmacist-led, multicomponent approaches; collaborative care; telephone-based counseling, care management, and reminders; and decision aids. Of these, educational interventions with behavioral support through continued patient contact over several weeks or months (effective for hypertension [122–124], hyperlipidemia [104–108], heart failure [128], and myocardial infarction [131]) and case management (effective for diabetes [95–97], hypertension [111, 112], heart failure [127], and depression [95, 96, 111, 140–142]) offer the most voluminous and consistent evidence of improvements in medication adherence and other health outcomes across varied clinical conditions. We also found moderate-strength evidence for self-management interventions for asthma, which generally include strong educational components. Other promising approaches found to be effective in more than 1 clinical area include reminders (heart failure, depression) (130, 152) and pharmacist-led, multicomponent approaches (heart failure, glaucoma) (129, 153), but this evidence is limited to single studies in each clinical area.

Certain intervention types may provide the most benefit for patients with a specific clinical condition. Collaborative care with in-person patient visits for education and counseling seemed to be effective primarily for patients with depression or with depression and diabetes; for other clinical conditions (hyperlipidemia and hypertension), the evidence was insufficient.

Some effective interventions, such as shared decision making (137) and blister packaging (110), that were tested in only a single clinical area with a single trial may hold promise, but without additional evidence, their widespread applicability is difficult to judge. Telephone counseling, care management, and monitoring, tested under 4 clinical conditions (diabetes [100], multiple sclerosis [154], depression [149–151], and musculoskeletal disease [158]), failed to show statistically significant benefit for medication ad-

herence, except in 1 trial for patients with multiple sclerosis (154).

Effect of Policy Interventions on Medication Adherence and Other Outcomes

Five studies evaluated effects of policy interventions on adherence to medications; all 5 addressed medications used to treat cardiovascular disease (**Appendix Table 4**) (163–167). Three of the 5 studies (163, 165, 167) also assessed adherence to medications used to treat diabetes, and 1 of the 5 studies (163) assessed adherence to medications used to treat respiratory conditions. One of the 5 studies was an RCT (166), whereas the other 4 were cohort studies. All 5 studies measured medication adherence by using insurance claims data as either the medication possession ratio or proportion of days covered. All 5 policy change interventions reduced patients' out-of-pocket expenses for prescription medications through either reduced medication copayments or improved prescription drug coverage.

All 5 studies found statistically significant between-group differences in adherence to medications for cardiovascular conditions, favoring patients whose medication copayments were reduced (163–166) or whose coverage improved (167). In 2 of the cohort studies (163, 164), however, medication adherence to cardiovascular medicines decreased over time in all groups, although the magnitudes of between-group differences were similar to those reported in the RCT (166). Together, these results provide moderate-strength evidence that policy interventions that reduce patient out-of-pocket expenses have a beneficial effect on adherence to cardiovascular medications (**Appendix Table 4**).

All 3 studies that assessed adherence to medications used to treat diabetes found statistically significant between-group differences in adherence to those medicines favoring the group that had reduced out-of-pocket expenses (163, 165, 167). In 2 of the 3 studies, medication adherence decreased over time in all groups. However, the magnitude of between-group differences was similar to that in the third study, which found an increase in adherence among those with some prior coverage for prescription medications after implementation of Medicare Part D (167). Therefore, we found moderate-strength evidence for policy interventions that reduced patient out-of-pocket expenses to improve adherence to medications used to treat diabetes (**Appendix Table 4**).

One study found no effect of a policy intervention on adherence to inhaled corticosteroids, which are usually used to treat reactive airway disease conditions (163). Therefore, we concluded that evidence is insufficient to draw conclusions for the effectiveness of policy interventions in this clinical area.

One trial examined the effect of policy interventions on clinical outcomes (166). It found a 14% reduction in the rate of first vascular events after hospital discharge for myocardial infarction. It also found a 26% reduction in total patient spending but no change in total insurer payments. We concluded that evidence is insufficient to draw conclusions about the effect of policy interventions on clinical and economic outcomes (**Appendix Table 4**).

Discussion

In this systematic review of patient, provider, systems, and policy interventions to improve medication adherence, we found evidence of effective interventions for many chronic conditions. Among interventions to improve medication adherence at the patient, provider, or systems level, we found the strongest evidence for improving medication adherence for self-management of asthma (in the short term) and case management or collaborative care with in-person patient education visits for depression. Among interventions to improve medication adherence at the policy level, we found robust evidence that reduced out-of-pocket expenses improved medication adherence across clinical conditions. With regard to clinical outcomes, we found the strongest evidence that improved medication adherence was accompanied by improved clinical outcomes with pharmacist-led hypertension management interventions for systolic blood pressure improvement and case management interventions for depression symptoms. We also found evidence that education with behavioral support; reminders; and pharmacist-led, multicomponent interventions enhanced adherence across more than 1 clinical area.

Our review is consistent with previous medication adherence reviews. A meta-analysis of intervention studies on medication adherence published through 1994 showed small to moderate effects of a broad range of behavioral interventions on medication adherence across multiple conditions (24), although the reviewers identified only 3 broad categories of intervention types (behavioral, educational, and "affective") and found no differences in outcomes by intervention type. The investigators did report that multidimensional approaches were more effective than unidimensional approaches (24). A Cochrane review of studies through 2007 also showed that medication adherence interventions can have moderate effects on adherence and health outcomes for several common chronic (as well as acute) medical conditions, although this review only included adherence studies that also assessed health outcomes (6).

Our review sought to broaden understanding of the effect of interventions on adherence. It included studies from 1994 through June 2012 with adherence intervention trials, even if they did not assess other health outcomes. Unlike other reviews, it examined intervention effects for specific clinical conditions and across conditions in relation to intervention type to identify those programs with the strongest evidence. It also included studies that assessed the effects of policy interventions.

Poor medication adherence produces large downstream health care costs. Thus, policymakers contemplat-

ing changes in health policy should take note of our assessment, from 5 consistent studies (moderate-strength evidence), that reducing patients' out-of-pocket costs improves medication adherence. Compared with other effective interventions, such as case management and collaborative care, which are relatively complex and labor-intensive, reducing copayments can potentially improve adherence for large numbers of geographically diverse patients.

Clinicians may be encouraged that the best evidence for improved medication adherence was present for several common conditions, including depression, hypertension, diabetes, asthma, and hyperlipidemia. However, it is also noteworthy that we found no studies that directly addressed polypharmacy and that we found either insufficient evidence or evidence of no benefit for studies of populations with multiple chronic conditions. Hence, caution must be used in extrapolating findings for 1 condition to patients with multiple comorbid conditions.

The 18 intervention clusters and characteristics we identified provide a starting framework by which practitioners and researchers may develop, test, and report their adherence programs more explicitly and consistently. The interventions we analyzed ranged from simple to complex. Decision-makers should be cautious in trying to pick components of complex interventions to enhance medication adherence. In our judgment, and as noted in a prior adherence review by Simoni and colleagues (22), sufficient information is not yet available to guide choices among the considerable array of program components. In our review, a lack of data about mediating relationships through which interventions affected adherence limited the conclusions that we could draw about the effectiveness of specific intervention components. Therefore, future studies should strive to more clearly describe each intervention component, and studies should be designed to identify which components are driving the effects of the intervention. For instance, more studies with factorial designs would help to assess both additive and multiplicative effects of intervention components. At a minimum, using guidelines from the Standards for Quality Improvement Reporting Excellence 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 (168).

Diverse interventions and varied adherence measures across studies limited our ability to pool results quantitatively. The identification and use of standardized, objective adherence measures and definitions in future research should enable investigators to pool data from such studies.

In addition to the heterogeneity of outcome measures noted, our review process and the evidence base both limit interpretations of our findings. The constraints for populations and settings that we imposed on the systematic review—such as excluding interventions for HIV, children and adolescents, and non-U.S. populations—limit its generalizability.

Although many studies were relatively small, they were conducted across many common chronic conditions affecting adults. Findings from this diverse set of clinical conditions and interventions have not been replicated in trials with larger patient populations or multiple study sites, in groups with different sociodemographic characteristics, or over longer follow-up periods. These gaps in the evidence base limit the applicability of our results.

We also limited our pool of included interventions to those designed specifically to address medication adherence as a primary or secondary outcome. We excluded clinical trials of drugs that assessed adherence to aid in the interpretation of safety and efficacy data. Thus, we did not address the comparative effectiveness of specific drug formulations in improving adherence.

We categorized patient, provider, and systems interventions by assigning labels based on short intervention descriptions that do not fully account for heterogeneity within and across clinical conditions or patient populations. Doing so allowed us to make comparisons across conditions but limited our ability to make definitive statements about intervention effectiveness across clinical areas. We believe our categories provide useful heuristics, but users should regard them more as hypothesis-generating than as an established system of classification.

Several reviews published over the past 2 decades, now complemented by our systematic review, confirm that a wide range of interventions can improve medication adherence. At this stage, new studies need to ask, "What specific elements of multicomponent interventions work best for improving medication adherence?" and, "How can we further enhance medication adherence interventions to increase adherence and ultimately improve health outcomes?"

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Note: RTI International is a trade name of Research Triangle Institute.

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Appendix Table 1. Inclusion and Exclusion Criteria

Category	Inclusion Criteria	Exclusion Criteria
Population	Adults prescribed self-administered medication for secondary or tertiary prevention of chronic diseases	Children younger than 18 years (no adults in the study or outcome of interest not stratified by child/adult); patients administered medications in hospitals or 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, and pelvic inflammatory disease); patients with mental illness involving psychosis, mania, or bipolar disorder; patients receiving medication to treat substance abuse
Geography	United States	All other countries
Period	1994 to present	Before 1994
Length of follow-up	No limit	–
Settings	Outpatient primary and specialty care settings, community-based, and home-based	Institutional settings (e.g., inpatient care, nursing homes, and prisons)
Interventions	Any intervention for included clinical conditions intended to improve adherence with prescribed, self-administered medications	Interventions intended to improve adherence with primary prevention measures (e.g., screening, diet, exercise, and lifestyle changes)
Outcomes	Medication adherence, biomarkers, mortality, morbidity, quality of life, patient satisfaction, health care use (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 on patient-level, provider-level, or systems-level interventions (study design and other criteria)	Original research (eligible study designs include randomized, controlled trials and systematic reviews, with or without meta-analyses)	Nonrandomized, controlled trials; observational study designs; case series; case reports; nonsystematic reviews; editorials; letters to the editor; articles rated high risk of bias; studies with historical, rather than concurrent, control groups; studies with <40 participants
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; and before–after studies)	Cross-sectional studies; case series; case reports; nonsystematic reviews; editorials; letters to the editor; articles rated high risk of bias; studies with <40 participants

Appendix Table 2. **Definitions of 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.

Appendix Table 3. **Summary of Strength of Evidence, by Intervention Type**

Intervention Type	Diabetes	Hyperlipidemia	Hypertension	Heart Failure	Myocardial Infarction	Asthma	Depression	Glaucoma	Multiple Sclerosis	Musculoskeletal Diseases	Multiple or Unspecified Conditions
Blister packaging	–	–	MA, persistence*: L (+)	–	–	–	–	–	–	–	–
Case management	MA: L (+)	–	MA: L (+)	MA: L (+)	–	–	MA: M (+)	–	–	MA: I	Persistence*: L (−)
Case management preceded by intensive interdisciplinary assessment	–	–	–	–	–	–	–	–	–	–	MA: I
Collaborative care (telephone and in person)	MA: L (+)	MA: I	MA: L (−)	–	–	–	MA: M (+)	–	–	–	–
Collaborative care (telephone only)	–	–	–	–	–	–	MA: I	–	–	–	–
Decision aids	–	MA: I	–	–	–	–	–	–	–	MA, persistence*, initiation of therapy: I	–
Education (face-to-face with pharmacist)	–	–	MA: L (+) Persistence*: I	–	–	–	–	–	–	–	–
Education and behavioral support (telephone, mail, and/or video)	–	MA: L (+)	MA: L (+)	MA: L (+)	MA: L (+) Persistence*: I	–	–	–	–	–	–
Education and social support	MA: I	–	MA: I	–	–	–	–	–	–	–	–
Health coaching	MA: I	–	–	–	–	–	–	–	–	–	–
Multicomponent interventions	–	MA: I	–	MA: L (+)	–	–	–	MA: L (+)	–	–	–
Pharmacist or physician access to patient adherence data	–	–	–	–	–	MA: L (−)	–	–	–	–	–
Patient access to medical records	–	–	–	MA: I	–	–	–	–	–	–	–
Reminders	–	–	–	MA: L (+)	–	–	MA: L (+)	–	–	–	–
Risk communication	–	–	MA: I	–	–	–	–	–	–	–	–
Self-management	–	–	–	–	–	MA: M (+)	–	–	–	–	–
Shared or clinical decision making	–	–	–	–	–	MA: L (+)	–	–	–	–	–
Telephone counseling, care management, and monitoring	MA: I	–	–	–	–	–	MA: I	–	MA: L (+)	MA: I	–
Virtual clinic	–	–	–	–	–	–	–	–	–	MA: L (+)	–

I = 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 (with respect to timing, dosage, or frequency as prescribed).

* In continuing treatment for the prescribed duration.

Appendix Table 4. **Summary of Evidence for Policy Interventions**

Clinical Condition	Intervention Type	Strength of Evidence for Medication Adherence	Studies/ Individuals, *n/N*	Results	Strength of Evidence for Other Outcomes	Studies/ Individuals, *n/N*	Results
Cardiovascular disease (163–167)	Improved prescription drug coverage*	Moderate-strength evidence of benefit	5/>70 000	Gaining coverage for cardiovascular medications: 13.4 to 13.5 MPR points Reduced copayment or improvement of previous coverage: range, −0.10 to 7.3 MPR/PDC points; median, 3.0 points (IQR, 2.5 to 4.4 points)	Insufficient for death from cardiovascular causes and composite outcome of rate of first vascular event or revascularization Insufficient for rate of first vascular event Low for patient total spending Low for insurer total spending	1/5855	Nonstatistically significant reduction in death from cardiovascular causes and composite outcome of rate of first vascular event or revascularization 14% decrease in rate of first vascular event 26% decrease in relative spending Nonstatistically significant decrease in relative spending
Diabetes (163, 165, 167)	Improved prescription drug coverage*	Moderate-strength evidence of benefit	3/20 000	Gaining coverage for diabetes medications: 17.9 MPR points Reduced copayment or improvement of previous coverage: range, 3.6 to 4.5 MPR points; median, 3.9 points (IQR, 3.7 to 4.3 points)	No evidence	No evidence	
Inhaled corticosteroids† (163)	Reduced medication copayment	Insufficient	1; NR	Effect not statistically significant	No evidence	No evidence	

IQR = interquartile range; MPR = medication possession ratio; NR = not reported; PDC = proportion of days covered.
* Includes all policy-level interventions that reduced patient out-of-pocket expenses for prescription drugs.
† Inhaled corticosteroids are usually used to treat reactive airway disease conditions, such as asthma and chronic obstructive pulmonary disease.

Appendix Figure. **Summary of evidence search and selection.**