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Interventions to Improve Medication Adherence
A Review

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IMPORTANCE Among adults with chronic illness, 30% to 50% of medications are not taken as prescribed. In the United States, it is estimated that medication nonadherence is associated with 125 000 deaths, 10% of hospitalizations, and $100 billion in health care services annually.

OBSERVATIONS PubMed was searched from January 1, 2000, to September 6, 2018, for English-language randomized clinical trials of interventions to improve medication adherence. Trials of patients younger than 18 years, trials that used self-report as the primary adherence outcome, and trials with follow-up periods less than 6 months were excluded; 49 trials were included. The most common methods of identifying patients at risk for nonadherence were patient self-report, electronic drug monitors (pill bottles), or pharmacy claims data to measure gaps in supply. Patient self-report is the most practical method of identifying nonadherent patients in the context of clinical care but may overestimate adherence compared with objective methods such as electronic drug monitors and pharmacy claims data. Six categories of interventions, and characteristics of successful interventions within each category, were identified: patient education (eg, recurrent and personalized telephone counseling sessions with health educators); medication regimen management (using combination pills to reduce the number of pills patients take daily); clinical pharmacist consultation for chronic disease co-management (including education, increased frequency of disease monitoring via telephone or in-person follow-up visits, and refill reminders); cognitive behavioral therapies (such as motivational interviewing by trained counselors); medication-taking reminders (such as refill reminder calls or use of electronic drug monitors for real-time monitoring and reminding); and incentives to promote adherence (such as reducing co-payments and paying patients and clinicians for achieving disease management goals). The choice of intervention to promote adherence will depend on feasibility and availability within a practice or health system. Successful interventions that are also clinically practical include using combination pills to reduce daily pill burden, clinical pharmacist consultation for disease co-management, and medication-taking reminders such as telephone calls to prompt refills (maximum observed absolute improvements in adherence of 10%, 15%, and 33%, respectively).

CONCLUSIONS AND RELEVANCE Adherence can be assessed and improved within the context of usual clinical care, but more intensive and costly interventions that have demonstrated success will require additional investments by health systems.

Supplemental content

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Among adults with chronic illness such as diabetes or hypertension, between 30% and 50% of medications are not taken as prescribed.[1,2] Poor adherence is associated with increased morbidity and mortality and may account for approximately 125 000 deaths and 10% of hospitalizations in the United States annually.[3-5] Nonadherence is also a significant contributor to health care costs: it is estimated that $100 billion annually is spent on US health care services that are directly related to poor medication adherence, such as successive hospitalizations and increased need for medical interventions.[6,7] Over the last 15 years, studies have been conducted in an effort to improve rates of medication adherence, but the rate of medication nonadherence has not appreciably improved.[1,2,8]

Medication-taking behavior is complex and involves patient, clinician, and health system factors. Patient factors that influence adherence include lack of involvement in the treatment decision-making process, poor health literacy, personal and community beliefs regarding medication effectiveness, and previous experiences with pharmacologic therapies (eg, adverse effects).[5] Clinician factors include failure to recognize nonadherence, prescription of complex and multidrug regimens, ineffective communication of benefits, and inadequate communication between prescribers (ie, specialists and primary care clinicians).[8] Health system factors include medication co-payments and poor coordination of care between inpatient and outpatient settings.[5] The multiplicity of reasons related to patient, clinician, and health system factors make nonadherence a challenging problem to address.

This review describes common methods to assess medication nonadherence in routine care and examines recent literature focusing on intervention strategies that have been tested to improve medication adherence. Potential strategies that clinicians and health systems should consider implementing based on current evidence are presented. The definition of medication adherence by Cramer et al[9] ("the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen") rather than persistence ("the duration of time from initiation to discontinuation of therapy") was used in this review, since most intervention trials had follow-up durations of 1 year or less. The term "adherence" rather than "compliance" was used because adherence better reflects the action required of the patient and because "noncompliance" has judgmental connotations.[10]

Methods

PubMed was searched for English-language randomized clinical trials, meta-analyses, and guidelines with Medical Subject Headings for medication adherence and measurement from January 1, 2000, to September 6, 2018 (additional details are reported in the eAppendix in the Supplement).

Trials were excluded if they included patients younger than 18 years; used self-report as the primary outcome of medication adherence (as opposed to clinical outcomes such as blood pressure levels or more objective measures of medication adherence, such as pharmacy refill data); had follow-up periods of less than 6 months; studied diseases requiring only short-term medication duration (ie, bacterial infections); did not report results using Consolidated Standards of Reporting Trials (CONSORT) criteria or similar standardized reporting methods; or involved interventions conducted outside the United States that would thus not be applicable to US clinicians because of differences in the ways patients procure, pay for, and monitor medications.

A taxonomy of behavior change techniques used in interventions for health promotion[11] and categories of interventions used in a recent systematic review[12] were consolidated to identify 6 categories of intervention strategies: patient education, medication regimen management, pharmacist-led interventions, cognitive behavioral therapies, medication-taking reminders, and incentives to promote adherence. Trials were selected for inclusion within each category, with consideration given to applicability of the intervention to the practicing clinician, information of interest to a general medical readership, and low risk of bias based on criteria developed by the Agency for Healthcare Research and Quality.[13] Trials selected for inclusion were mutually agreed on by the 2 review authors, and disagreements were resolved through discussion.

Observations

Assessing Medication Nonadherence

Among the 49 trials included in this review, the most common methods of assessing nonadherence were through pharmacy claims data on missed medication fills or refills (23 trials), electronic drug monitors (14 trials), and patient self-report (9 trials that also included a clinical marker such as blood pressure). Sensitivity and specificity of medication adherence assessment methods are uncommonly reported owing to lack of consensus on a "gold standard" method, as well as an established cutoff for defining nonadherence (a review of patient self-report scales found that only 12 of 43 measures reported sensitivity and specificity).[14] The advantages and drawbacks of each method, correlations between adherence assessments and clinical outcomes, and correlations among the adherence assessment methods are described below.

Electronic Drug Monitoring

Electronic monitors that detect and record the opening of pill bottles to measure adherence are a common method of identifying nonadherent patients and were used in 14 trials included in this review. Studies of commercially available devices demonstrate that electronic drug monitors are accurate in measuring the opening of pill bottles (and therefore presumed medication ingestion),[15,16] and several studies have shown moderate to strong associations between electronically monitored adherence and improvement in clinical biomarkers.[17-19] Arnsten et al[17] found that among 67 patients with HIV, correlation between higher adherence and improved HIV viral load ranged from $r = 0.46$ to $r = 0.60$ ($P < .001$), depending on the definitions of adherence used. Liu et al[18] found that among 108 patients with HIV, mean adherence measured by electronic drug monitors was 74% among patients with undetectable viral load and 49% among patients with detectable viral load ($P = .002$). Despite the association between electronically monitored adherence and clinical outcomes, the cost of the monitors and the challenges of integrating their adherence data into clinical care may be barriers to their routine use outside of the research setting.

Pharmacy Claims Data

Pharmacy data were used in 23 trials to identify patients who did not fill prescriptions or refills. Most commonly, studies defined nonadherent patients as those who did not fill initial prescriptions within 2 weeks or who refilled less than 80% of their prescriptions over 1 year. Pharmacy claims provide reliable information on cumulative medication exposure and gaps[20] and are associated with improvements in clinical biomarkers (a 10% decrease in adherence to statins was associated with a mean increase of 4.9 mg/dL in low-density lipoprotein cholesterol [LDL-C] concentration in 1 study [to convert LDL-C values to mmol/L, multiply by 0.0259]).[21] Adherence measured by pharmacy claims is moderately correlated with adherence measured by electronic drug monitors. For example, Choo et al[20] found that among 286 members of a managed care organization taking monotherapy for hypertension, the proportion of doses consumed as measured by electronic pill bottles was moderately correlated with the proportion of days for which there was adequate supply of medication determined from pharmacy dispensing records (92% vs 97%; r = 0.32 [P < .001]). However, adherence measured by pharmacy claims may not be as strongly predictive of clinical outcomes compared with electronic pill bottles, since pharmacy claims may not necessarily reflect the medications patients actually ingest. A recent study found that the association between adverse clinical outcomes after acute myocardial infarction and adherence measured by electronic drug monitors vs pharmacy claims data was similar (hazard ratio, 0.48 [95% CI, 0.22-0.81] vs 0.42 [95% CI, 0.26-0.88], respectively), but there was a slight improvement in model fit using electronic drug monitors compared with pharmacy claims (Bayesian information criterion values,811 vs 803; P = .05).[22] An advantage of using pharmacy data to identify nonadherent patients is that it may be scalable and implemented into the clinical workflow, since many health systems already link their electronic health records with pharmacies.

Patient Self-report

Self-reported medication adherence is a practical way to measure adherence because of its low cost and potential to be easily implemented into the clinical workflow. Evidence showed that self-reported adherence was predictive of clinical outcomes. Associations between self-reported adherence rates and improvement in clinical biomarkers such as HIV viral load or hemoglobin A_{1c} concentration ranged between 43% to 84% in meta-analyses.[23] In a meta-analysis of 65 studies (n = 15 351) of patients with HIV that used self-reported measures of adherence (ie, survey questionnaires or interviews), patients who self-reported nonadherence at any cutoff level were 2.3 times more likely to have a detectable HIV viral load compared with patients who self-reported high adherence.[24]

Gehi et al[25] asked 1015 patients with coronary artery disease a single screening question: "In the past month, how often did you take your medications as the doctor prescribed?" Patients who reported adherence of 75% or less were 2.3 times more likely to have myocardial infarction, stroke, or cardiovascular death at 5 years of follow-up compared with patients who reported greater than 75% adherence. While self-reported adherence is moderately correlated with objective measures of adherence, it tends to overestimate adherence. Garber et al[26] conducted a review of 57 studies that compared self-reported adherence with objective measures of adherence (86 total comparisons). While 37 of the comparisons were concordant, self-report produced higher estimates of adherence compared with other methods in 45 of the 49 remaining comparisons.

In a meta-analysis of 11 studies (n = 1684 patients) by Shi et al,[27,28] the pooled correlation coefficient of self-report compared with electronic drug monitoring was 0.45 [95% CI, 0.34-0.56], but self-reported rates of adherence were higher than rates of adherence measured by electronic drug monitors (84% vs 75%).

Choosing an Intervention to Improve Adherence

Once nonadherence is identified, clinicians should choose 1 or more of the following interventions based on each patient's individual barriers to adherence (eg, difficulty remembering to take medications or difficulty paying for medications) and the specific resources available within the practice or health system. A summary of the 49 individual randomized clinical trials included in this review is provided in **Table 1**.

Patient Education

Educational interventions that are personalized, repeated, and initiated at the time of new disease diagnosis have shown modest success in improving adherence. For example, Nieuwkerk et al[33] randomized 201 patients newly prescribed statins to receive educational sessions on each patient's individualized risk of cardiovascular events with and without treatment. The intervention group demonstrated an improvement in mean LDL-C concentration at 6 months relative to the control group (from 186 to 103 mg/dL in the intervention group vs 189 to 116 mg/dL in the control group; difference in differences, 10 mg/dL). Another example is the study by Stacy et al[30] that randomized 497 patients newly prescribed statins to receive an educational intervention based on an individual patient's cholesterol-related knowledge, beliefs, and barriers to adherence vs a mailed educational cholesterol guide that was not individualized. The proportion of patients classified as adherent was higher in the intervention group relative to the control group at 6 months (from 72% to 70% in the intervention group vs 74% to 61% in the control group; difference in differences, 11%).

Other studies have tested the effect of telephone counseling interventions conducted by nurses or trained health educators on disease management and adherence. The studies that demonstrated success (Walker et al[32] reported a small but statistically significant reduction in hemoglobin A_{1c} concentration from 8.6% to 8.3%; Rinfret et al[35] reported a small but statistically significant increase in refill adherence from 90% to 99%) initiated sessions within 1 month of disease diagnosis or at medication treatment initiation and used repeated sessions (10 and 4 calls per year in the studies by Walker et al and Rinfret et al, respectively). The association of observed improvements in concentrations of LDL-C and hemoglobin A_{1c} with clinical outcomes was not assessed.

The studies that reported no effect on adherence delayed the start of the intervention longer than 1 month after diagnosis (Eussen et al[31] and Solomon et al[34] or used only a 1-time telephone call (O'Connor et al[36]). These trials suggest that clinicians may improve adherence by educating patients about their personalized risks with and without therapy at the time of disease diagnosis and by conducting follow-up telephone calls (using clinic support staff if available) to reinforce risks of nonadherence. However, providing timely

Table 1. Summary of Individual Randomized Clinical Trials, by Intervention Strategy

Source	Disease	Intervention Details	Comparison Group	Adherence or Outcome Measure	Effect Size (Intervention Group)
Patient Education					
Laporte et al,[29] 2003	Venous thromboembolism (n = 86)	Intensive, daily, in-hospital education	Usual predischarge counseling	INR	No difference in INR levels at 1 y
Stacy et al,[30] 2009	Dyslipidemia (n = 497)	Interactive telephone call with individualized feedback on cholesterol knowledge	Mailed, nonindividualized cholesterol guide	Pharmacy claims	Proportion of patients who refilled statin prescriptions was higher in intervention group (72% to 70% in intervention group vs 74% to 61% in control group; difference in differences, 11%) at 6 mo
Eussen et al,[31] 2010	Dyslipidemia (n = 899)	Five individual educational sessions on the importance of adherence for lipid levels	Usual care	Pharmacy claims	No difference in refills at 1 y
Walker et al,[32] 2011	Diabetes (n = 526)	Ten interactive telephone counseling calls by trained health educators	Printed, nonindividualized diabetes guide	Hemoglobin A_{1c}	Improvement in mean hemoglobin A_{1c} concentration (from 8.6% to 8.3% in intervention group vs 8.7% to 8.7% in control group; difference in differences, 0.3%) at 1 y
Nieuwkerk et al,[33] 2012	Dyslipidemia (n = 201)	Individualized educational session on personalized risk of cardiovascular events with and without treatment	Usual care	LDL-C	Improvement in mean LDL-C concentration (from 186 to 103 mg/dL in intervention group vs 189 to 116 mg/dL in control group; difference in differences, 10 mg/dL) at 6 mo
Solomon et al,[34] 2012	Osteoporosis (n = 1046)	Ten telephone counseling sessions with health educators on specific osteoporosis topics	Mailed educational materials	Pharmacy claims	No difference in refills at 1 y
Rinfret et al,[35] 2013	CAD (n = 300)	Four telephone calls by nurses to reinforce importance of adherence	Usual care	Pharmacy claims	Proportion of patients who picked up >80% of refills improved from 90% in control group to 99% in intervention group at 1 y
O'Connor et al,[36] 2014	Diabetes (n = 2378)	One scripted telephone call from diabetes educator to identify and address nonadherence	Usual care	Pharmacy claims	No difference in refills at 1 y
Granger et al,[37] 2015	Heart failure (n = 86)	Intensive predischarge education by nurses on medication goals and response plans	Usual predischarge counseling	Pill counts	Proportion of patients who took >80% of their pills increased from 32% to 70% in intervention group vs 28% to 33% in control group at 1 y
Medication Regimen Management					
Thom et al,[38] 2013	Cardiovascular risk factors (n = 2004)	Once-daily fixed-dose combination pill of aspirin, a statin, and 2 antihypertensive medications	Usual medication regimen	Blood pressure, LDL-C	Improvement in mean systolic blood pressure (from 137 to 129 mm Hg in intervention group vs 137 to 132 mm Hg in control group; difference in differences, 3 mm Hg) and in LDL-C concentration (from 92 to 84 mg/dL in intervention group vs 93 to 88 mg/dL in control group; difference in differences, 3.2 mg/dL) at 15 mo
Castellano et al,[39] 2014	Myocardial infarction (n = 2118)	Once-daily fixed-dose combination pill of aspirin, a statin, and 2 antihypertensive medications	Usual medication regimen	Pill counts	Proportion of patients who took >80% of their pills improved from 41% in control group to 51% in intervention group at 9 mo
Selak et al,[40] 2014	Cardiovascular risk factors (n = 513)	Once-daily fixed-dose combination pill of aspirin, a statin, and 2 antihypertensive medications	Usual medication regimen	Blood pressure, LDL-C	No difference in blood pressure or LDL-C concentration at 12 mo
Messerli et al,[41] 2016	Polypharmacy (n = 450)	Two sequential medication reviews ("polymedication check") in patients who used >4 medications/d	A single medication review in patients who used >4 medications/d	Pharmacy claims	No difference in refills at 6 mo
Clinical Pharmacist Consultation					
Magid et al,[42] 2011	Hypertension (n = 283)	Pharmacist-led education, home blood pressure monitoring, blood pressure reporting to automated telephone calls, and pharmacist follow-up	Usual care	Blood pressure	Improvement in mean systolic blood pressure (from 150 to 137 mm Hg in intervention group vs 144 to 137 mm Hg in control group; difference in differences, 6 mm Hg) at 6 mo
Calvert et al,[43] 2012	CAD (n = 143)	Education, communication, and assessment by community-based pharmacists	Usual care	Pharmacy claims	No difference in refills at 6 mo
Heisler et al,[44] 2012	Hypertension (n = 4100)	Pharmacist-led education, counseling on barriers to adherence and targets for blood pressure, and medication titration	Usual care	Blood pressure	Improvement in mean systolic blood pressure (from 148 to 146 mm Hg in intervention group vs 148 to 148 mm Hg in control group; difference in differences, 2.4 mm Hg) at 3 mo; no difference at 14 mo

(continued)

Table 1. Summary of Individual Randomized Clinical Trials, by Intervention Strategy (continued)

Source	Disease	Intervention Details	Comparison Group	Adherence or Outcome Measure	Effect Size (Intervention Group)
Ho et al,[45] 2014	Myocardial infarction (n = 241)	Pharmacist-led education, medication review and titration, and refill reminders	Usual care	Pharmacy claims, blood pressure, LDL-C	Proportion of patients who picked up >80% of refills improved from 74% in control group to 89% in intervention group at 1 y; no difference in blood pressure or LDL-C concentration
Stewart et al,[46] 2014	Hypertension (n = 395)	Pharmacist-led home blood pressure monitoring, motivational interviewing, medication review, and reminder calls	Usual care	Pharmacy claims	Improvement in mean systolic blood pressure (from 142 to 132 mm Hg in intervention group vs 140 to 135 mm Hg in control group; difference in differences, 5 mm Hg) at 6 mo
Hedegaard et al,[47] 2015	Hypertension (n = 532)	Pharmacist-led education, medication review and titration, counseling, and telephone follow-up	Usual care	Pharmacy claims, composite end point of cardiovascular events	Proportion of patients who picked up >80% of refills improved from 70% in control group to 80% in intervention group at 1 y; no difference in cardiovascular events
Cognitive Behavioral Interventions					
Ogedegbe et al,[48] 2008	Hypertension (n = 190)	Four 30-min motivational interviewing sessions delivered by trained research assistants over 1 y	Usual care	Electronic pill bottles, blood pressure	Proportion of patients who took doses as scheduled improved from 43% in control group to 57% in intervention group at 1 y; no difference in blood pressure at 1 y
Apter et al,[49] 2011	Asthma (n = 333)	Four sessions of problem-solving training (defining barriers to adherence, weighing solutions, revising) delivered by trained research coordinators	Usual care	Electronic inhaler monitor	No difference in adherence at 6 mo
Wu et al,[50] 2008	Heart failure (n = 82)	Four sessions of theory of planned behavior counseling delivered by a nurse specialist	Usual care	Electronic pill bottles	Proportion of patients classified as adherent (took >88% of pills) improved from 36% in control group to 74% in intervention group at 9 mo
Chisholm-Burns et al,[51] 2013	Kidney transplant (n = 150)	Four sessions reviewing a signed behavioral contract involving goal-setting, motivation, and memory techniques delivered by a trained pharmacist	Usual care	Pharmacy claims	Proportion of patients who refilled medications on schedule improved from 79% in control group to 89% in intervention group
Goggin et al,[52] 2013	HIV (n = 204)	Ten sessions of motivational interviewing delivered by trained counselors	Usual care	Electronic pill bottles	No difference in adherence at 1 y
Gross et al,[53] 2013	HIV (n = 180)	Four in-person and 12 telephone counseling sessions in problem-solving theory delivered by trained counselors	Usual care	Electronic pill bottles	Proportion of patients who took >70% of pills improved from 35% in control group to 50% in intervention group at 1 y
O'Carroll et al,[54] 2013	Stroke (n = 62)	Two sessions of habitual behavior training delivered by a trained research fellow	Usual care	Electronic pill bottles	Proportion of patients who took doses as scheduled improved from 87% in control group to 97% in intervention group at 6 mo
Insel et al,[55] 2016	Hypertension (n = 128)	Four training sessions in cognitive behavioral techniques to promote habitual medication-taking, delivered by trained nurses	Usual care	Electronic pill bottles	No difference in adherence at 6 mo
Reese et al,[56] 2016	Dyslipidemia (n = 120)	Social forces interventions (weekly messages comparing adherence rates with those of other patients)	Usual care	Electronic pill bottles	No difference in adherence at 6 mo
de Bruin et al,[57] 2017	HIV (n = 221)	Four sessions of training in self-management strategies delivered by trained nurses	Patient information leaflet	Viral load	Improvement in mean viral load, 10 copies/mL at 15 mo (from 45 to 35 copies/mL)
Dobbels et al,[58] 2017	Heart, liver, or lung transplant (n = 205)	Four sessions of social cognitive theory, motivational interviewing, and adherence feedback	Usual care	Electronic pill bottles	Proportion of patients who took doses as scheduled improved from 79% in control group to 95% in intervention group at 1 y
Reminders (Text Messages, Telephone Calls, Devices)					
Tamblyn et al,[59] 2010	Hypertension or dyslipidemia (n = 2293)	Automated tracking of refills in the electronic health record and email alerts to clinicians for missed refills	Usual care	Pharmacy claims	No difference in refill adherence at 6 mo
Vollmer et al,[60] 2011	Asthma (n = 8517)	Automated, interactive voice recognition telephone calls to prompt refills of inhaled corticosteroids	Usual care	Pharmacy claims	Proportion of patients who picked up >80% of refills improved from 40% in control group to 42% in intervention group at 6 mo
Kripalani et al,[61] 2012	CAD (n = 435)	Refill reminder postcards and an illustrated daily medication schedule	Usual care	Pharmacy claims	No difference in refill adherence at 1 y
Odegard and Christensen,[62] 2012	Diabetes (n = 265)	Pharmacist reminder calls to patients 6 d late to refill oral diabetes medications	Usual care	Pharmacy claims	Proportion of patients who picked up >80% of refills improved from 85% in control group to 90% in intervention group at 1 y

(continued)

Table 1. Summary of Individual Randomized Clinical Trials, by Intervention Strategy (continued)

Source	Disease	Intervention Details	Comparison Group	Adherence or Outcome Measure	Effect Size (Intervention Group)
Derose et al,[63] 2013	Dyslipidemia (n = 5216)	Reminder call followed by reminder letter among patients newly prescribed statins who had not filled the prescription within 1 week	No reminder call or letter	Pharmacy claims	Proportion of patients who picked up initial prescriptions improved from 26% in control group to 43% in intervention group within 2 weeks of reminder call
Pinnock et al,[64] 2013	COPD (n = 256)	Daily interactive telemonitoring of symptoms and treatment use, with alerts for omitted readings	Usual care	Hospitalization for COPD exacerbation	No difference at 1 y
Vervloet et al,[65] 2014	Diabetes (n = 104)	Electronic pill bottle monitoring with text message reminders sent only if patients missed doses	Electronic pill bottle monitoring alone	Electronic pill bottles	Proportion of patients who took doses as scheduled improved from 70% in control group to 81% in intervention group at 6 mo
Vollmer et al,[66] 2014	Cardiovascular disease (n = 21 752)	Refill reminders (calls plus letters), live outreach educational calls, feedback to primary clinicians	Usual care	Pharmacy claims	Proportion of patients who picked up >80% of refills improved from 55% in control group to 58% in intervention group at 1 y
Bobrow et al,[67] 2016	Hypertension (n = 1372)	Adherence support text messages on developing habits, social support, and natural consequences	Written information on hypertension	Blood pressure	Improvement in mean systolic blood pressure (from 135 to 132 mm Hg in intervention group vs 135 to 134 mm Hg in control group; difference in differences, 2.2 m Hg) at 1 y
Choudhry et al,[68] 2017	Chronic disease (1-3 daily medications) (n = 480)	One of 3 pill bottles (strip with toggles, digital timer cap, or standard pill box)	No device	Pharmacy claims	No difference in refill adherence at 1 y
Cook et al,[69] 2017	Glaucoma (n = 201)	Electronic pill bottle monitoring with monthly telephone calls to inquire about missed doses	Electronic pill bottle monitoring and monthly motivational interviewing	Electronic pill bottles	Proportion of patients who took doses as scheduled improved from 76% in control group to 83% in intervention group at 6 mo
Dai et al,[70] 2017	Chronic disease (≥1 daily medication) (n = 581)	Monthly mailings of basic reminders, reminders with adherence prediction, or reminders with adherence commitments	Standard mailings from insurer	Pharmacy claims	Proportion of patients who picked up >80% of refills improved from 61% in control group to 62% in intervention group at 6 mo, driven by the basic and commitment reminders
Reese et al,[71] 2017	Kidney transplant (n = 120)	Electronic pill bottle monitoring with customized reminders and clinician notification if adherence <90%	Electronic pill bottle monitoring alone	Electronic pill bottles	Proportion of patients who took doses as scheduled improved from 55% in control group to 88% in intervention group at 6 mo
Incentives to Promote Adherence					
Choudhry et al,[72] 2011	Myocardial infarction (n = 5855)	Full prescription coverage (eliminating all out-of-pocket costs for medications)	Usual prescription coverage	Pharmacy claims and first major vascular event	Proportion of patients who picked up >80% of refills improved from 39% in control group to 44% in intervention group at 1 y; reduction in the rate of total major vascular events or revascularization from 23% to 21% per 100 person-years at 1 y
Kimmel et al,[73] 2012	Chronic anticoagulation (n = 100)	Daily lottery-based incentive (expected daily value of $3 if adherent)	No incentive	INR	No overall difference in INR at 6 mo; reduction in out-of-range INR among subgroup with baseline subtherapeutic INR
Priebe et al,[74] 2013	Psychotic illness (n = 131)	$22 per monthly depot antipsychotic injection	No incentive	Direct observance	Proportion of patients who took doses as scheduled improved from 71% in control group to 85% in intervention group at 1 y
Asch et al,[75] 2015	Dyslipidemia (n = 1503 patients, n = 340 clinicians)	Clinician, patient, or shared clinician-patient financial incentives ($1024 total) to achieve LDL-C goals	No incentive	LDL-C	Improvement in mean LDL-C concentration in shared clinician-patient incentive group (from 160 to 126 mg/dL in intervention group vs 162 to 136 mg/dL in control group; difference in differences, 8.5 mg/dL) at 1 y
Volpp et al,[76] 2015	Hypertension (n = 337)	$8 per medication per month paid at prescription refill, and a computerized behavioral incentive	Usual care	Pharmacy claims	No difference in refill adherence at 1 y

Abbreviations: CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; INR, international normalized ratio; LDL-C, low-density lipoprotein cholesterol.

SI conversion factor: To convert LDL-C values to mmol/L, multiply by 0.0259.

and sustained interventions within the clinical workflow may be challenging for many clinicians.

Medication Regimen Management

Four trials examined the effect of adjusting medication regimens (using combination pills to reduce the number of pills patients take daily) on medication-taking behavior. Simplifying medication regimens by maximizing doses of 1 medication before starting another and using combination pills when available can improve adherence. Thom et al[38] and Castellano et al[39] randomized 2004 and 2118 patients, respectively, at risk of cardiovascular events to receive a fixed-dose combination (single pill) of aspirin, a statin, and 2 antihypertensive medications, vs the usual 4 pills. Patients who received the fixed-dose combination had an adherence increase from

41% to 51% (Castellano et al[39]), mean reductions in systolic blood pressure from 137 to 129 mm Hg in the intervention group vs 137 to 132 mm Hg in the control group (difference in differences, 2.6 mm Hg) (Thom et al[38]), and mean reductions in LDL-C concentration from 92 to 84 mg/dL in the intervention group vs 93 to 88 mg/dL in the control group (difference in differences, 3.2 mg/dL) at 15 months (Thom et al[38]). However, the associations of improvements in blood pressure and LDL-C concentration with clinical outcomes were not assessed. These trials suggest that clinicians can improve adherence by reducing patients' daily pill burden when possible. This intervention also had potential to be integrated into the clinical workflow (ie, by displaying available combination pills within each patient's electronic health record).

Clinical Pharmacist Consultation

Clinical pharmacists can improve adherence and management of chronic diseases through chronic disease co-management. Many studies have tested the effect of pharmacist-led multicomponent interventions compared with usual care among patients with hypertension. The studies by Magid et al (n = 283),[42] Stewart et al (n = 396),[46] Ho et al (n = 241),[45] and Hedegaard et al (n = 532)[47] included the following components: (1) pharmacist clinic visit with education on blood pressure goals, (2) home blood pressure monitoring and reporting of blood pressure measurements either via telephone or an in-person follow-up visit, (3) medication adjustment based on home measurements, and (4) medication refill reminder telephone calls. Compared with controls, patients in the intervention group had lower mean systolic blood pressure measurements (from 150 to 137 mm Hg in the intervention group vs 144 to 137 mm Hg in the control group [difference in differences, 6 mm Hg] in the study by Magid et al[42] and from 142 to 132 mm Hg in the intervention group vs 140 to 135 mm Hg in the control group [difference in differences, 5 mm Hg] in the study by Stewart et al[46]). However, the effect on clinical outcomes was not studied. In the studies by Ho et al[45] and Hedegaard et al,[47] there were no differences in blood pressure or clinical outcomes, although the intervention groups had significant increases in refills (from 74% to 89% and from 70% to 80%, respectively). Although not all trials demonstrated consistent clinical improvements, the evidence suggests that clinicians can improve adherence and potentially disease control by referring patients to clinical pharmacists for disease co-management, if available within their practice or health system."

Cognitive Behavioral Therapy

Cognitive behavioral interventions such as motivational interviewing, planned behavior education, or self-management strategies can improve adherence. For example, de Bruin et al[57] and Gross et al[53] randomized 221 and 180 patients, respectively, with HIV to receive multiple sessions of in-person training in self-management strategies delivered by trained nurses or counselors. In the study by de Bruin et al,[57] the intervention group had a lower mean viral load of 10 copies/mL (from 45 copies/mL to 35 copies/mL) at 15 months. In the study by Gross et al, the proportion of patients classified as adherent (taking >70% of their medication) improved from 44% to 50% in the intervention group vs 39% to 35% in the control group at 1 year. The effect of these improvements on clinical outcomes was not studied.

A recent meta-analysis found that among 11 studies (n = 2529 patients) that used an objective measure of adherence, motivational interviewing was associated with a small increase in medication adherence (pooled risk ratio for adherence, 1.13 [95% CI, 1.01-1.28]).[77] The most successful interventions were delivered by trained counselors and involved multiple sessions (studies of successful interventions by de Bruin et al,[57] Gross et al,[53] Wu et al,[50] Chisholm-Burns et al,[51] Ogedegbe et al,[48] and Dobbels et al[58] each used 4 in-person sessions). However, most of the trials that tested motivational interviewing targeted adherence to highly active antiretroviral therapy, and many were conducted in patients who had concurrent psychosocial conditions, such as depression, that may limit the generalizability of these interventions. Clinicians could consider referring selected patients with nonadherence for cognitive behavioral therapy, if cognitive behavioral therapy was available within their practice or health system. However, these trials suggested that adherence is unlikely to improve unless such interventions are delivered by trained specialists over at least 4 sessions, raising concerns about feasibility and scalability.

Medication-Taking Reminders

Thirteen studies tested the effect of medication-taking reminders (text messages, telephone calls, and/or devices such as electronic drug monitors) on adherence. Text message or telephone call reminders are most effective when they are personal or interactive, rather than generic or prerecorded. For example, Vollmer et al[60] randomized 8517 patients to a personal telephone call to prompt refills, and Bobrow et al[67] randomized 1372 patients to an interactive text intervention to prompt medication refills. Vollmer et al found a 2% improvement in adherence (from 40% to 42%) to inhaled corticosteroids among patients with asthma, while Bobrow et al found an improvement in mean systolic blood pressure (from 135 to 132 mm Hg in the intervention group vs 135 to 134 mm Hg in the control group; difference in differences, 2 mm Hg). However, these improvements were small and may not translate into clinically important effects.

Refill reminders may be most effective when they are targeted to patients who do not fill a new prescription at the time of disease diagnosis. Derose et al[63] randomized 5216 patients with a first-time statin prescription who did not pick up the medication within 1 week to receive a telephone reminder and a personalized letter emphasizing the importance of statin therapy to prevent heart attack and stroke. Seventeen percent more patients (43% in the intervention group vs 26% in the control group) filled the initial prescription within 2 weeks of the reminder call. In a recent meta-analysis of 16 trials of text message reminders (n = 2742), the pooled odds of adherence was 1.68 [95% CI, 1.18-2.39] times higher in the intervention group.[78] However, the meta-analysis included studies that used self-report as an adherence outcome, which may have overestimated the intervention effect.

In contrast, electronic drug monitors are unlikely to improve adherence without additional support from clinicians or the health system. Choudhry et al[68] randomized 53 480 patients taking 1 to 3 chronic medications to usual care, a standard pillbox, a pill bottle with a digital timer cap displaying the time elapsed since the medication was last taken, or a pill bottle strip with toggles that can be slid after each day's dose has been taken and found no difference in adherence between any of the groups. However, electronic drug monitors

may be effective when they are used to measure missed doses and deliver reminders by text or telephone. Vervloet et al[65] randomized 104 patients with diabetes and poor adherence to electronic drug monitors and text message reminders for missed doses, drug monitors alone, or usual care. At 2 years of follow-up, the group receiving monitoring and text messages took 11% more pills (from 70% to 81%) compared with the other groups. Reese et al[71] randomized 120 kidney transplant recipients to receive electronic pill bottles with personalized reminders and physician notification if adherence was less than 90%, vs electronic pill bottles alone. The proportion of patients who took doses as scheduled improved from 55% in the control group to 88% in the intervention group at 6 months. However, it is unknown whether these improvements in adherence were associated with clinically meaningful benefit in outcomes. These studies suggested that clinicians could improve adherence with interactive or personal refill reminders, particularly when delivered to patients who did not fill new prescriptions at the time of disease diagnosis. Electronic drug monitors with automated reminders may also be effective, although many practices and health systems may not have the infrastructure or resources available to provide them to nonadherent patients.

Incentives to Promote Adherence

Studies that tested the effect of financial incentives on medication-taking behavior have yielded mixed results. Asch et al[75] randomized 343 primary care physicians and 1503 of their patients who were prescribed statins to receive physician financial incentives, patient financial incentives, or shared physician-patient incentives to achieve goal LDL-C concentrations. Patients in the shared physician-patient incentives group achieved greater reduction in LDL-C concentrations (from 160 to 126 mg/dL in the intervention group vs 162 to 136 mg/dL in the control group; difference in differences, 8.5 mg/dL). However, no clinical end points such as hospitalization or mortality were studied. Volpp et al[76] randomized 337 patients prescribed antihypertensive medications to receive $8 per medication per month for filling prescriptions, a computerized behavioral intervention, both the financial incentive plus the behavioral intervention, or usual care. There was no difference in medication adherence or blood pressure between any of the groups.

Prescribing medications with the lowest patient co-payments may also be effective. Choudhry et al[72] randomized 5855 patients discharged after hospitalization for acute myocardial infarction to receive full prescription coverage (zero out-of-pocket costs) vs usual coverage for all statins, β-blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers. Rates of medication adherence improved from 39% in the control group to 44% in the intervention group, and there was a lower rate of total major vascular events or revascularization, from 23% to 21% per 100 person-years at 1 year. However, the magnitude of improvement was small and may not be clinically meaningful. These trials suggested that financial incentives have the potential to improve adherence. The feasibility and scalability of this approach to improve adherence is a barrier, and most clinicians and health systems will not have the resources to provide significant incentives to improve adherence. However, incentives to promote health are available in real-world practice in the form of employer-based contracts with insurance companies. Some of these contracts provide incentives to promote healthy behavior and adherence, such as a lottery ticket each time a patient refills a medication. If available, these could be reasonable tools to improve adherence.

A summary of interventions is provided in **Table 2**.

Discussion

Available evidence suggests that there are effective strategies that clinicians and health systems can implement to identify nonadherent patients and improve adherence to medications. Because of the wide heterogeneity in diseases, outcomes, and interventions studied, some caution is warranted in trying to select the "most effective" intervention that clinicians should use. Rather, the choice of intervention or interventions should depend on availability and feasibility within a given practice or health system. A summary of recommendations is provided in **Table 3**.

Clinicians and health systems can implement several strategies to identify and improve medication adherence. Self-report is likely to be the most practical method of assessing adherence in the context of clinical care but may overestimate adherence. The choice of intervention to improve adherence will depend on availability within a practice or health system, but clinically practical and successful strategies to promote adherence include using combination pills to reduce daily pill burden, clinical pharmacist consultation for disease co-management, and medication-taking reminders such as telephone calls to prompt refills. Hospitals and health systems could consider investments in more intensive but costly strategies (such as recurrent counseling sessions with health educators or reduction/elimination of medication co-payments) to improve medication nonadherence.

Since reasons for medication nonadherence are complex and include patient, clinician, and health system factors, it may be helpful to view the problem of nonadherence through the social-ecological framework for health promotion.[79] This framework posits that achieving change requires acting simultaneously across multiple perspectives. Ideally, the interventions outlined in this review could occur together rather than in isolation, but this will require sustained efforts and investments by clinicians, health systems, and policy makers. Although the improvements in clinical markers such as blood pressure and LDL-C concentration observed in many of the trials were small, epidemiologic studies and meta-analyses suggest that even incremental improvements in blood pressure or LDL-C concentration are associated with reductions in morbidity and mortality at a population level.[80,81] Thus, if these improvements in adherence and intermediate clinical outcomes are realized on a population level, they may produce important benefits to population health. In the MI-FREEE (Post-Myocardial Infarction Free Rx Event and Economic Evaluation) study by Choudhry et al,[72] an improvement of 5% in medication adherence to cardiovascular medications after myocardial infarction was associated with a 2% absolute reduction in total major vascular events or revascularization over 1 year of follow-up.

Clinicians should not be solely responsible for identifying and intervening for nonadherent patients. Rather, effective interventions for treating adherence require a team. Certain procedures could be routinely implemented into the clinical encounter by

Table 2. Summary of Interventions to Improve Adherence

Description	Example	Maximum Observed Effect	Advantages	Disadvantages
Patient Education				
Assess and address barriers to adherence Educate patients about their individual risk of disease-related complications with and without therapy at the time of disease diagnosis Follow-up telephone calls (using clinic support staff if available) to reinforce importance of medications and inquire about adherence Emphasize the importance of medications to slow disease progression at every visit	For a patient newly prescribed a statin, use an online calculator to show his or her individualized risk of cardiovascular events with and without treatment	Clinical: In Niuewkerk et al,[33] improvement in mean LDL-C concentration (from 186 to 103 mg/dL in intervention group vs 189 to 116 mg/dL in control group; difference in differences, 10 mg/dL) at 6 mo Adherence: In Granger et al,[37] proportion of patients who took >80% of their pills increased from 32% to 70% in intervention group vs 28% to 33% in control group at 1 y	Available, feasible, and generally acceptable to patients	Significant time and additional health care personnel required to deliver personalized and repeated educational sessions The clinical significance of these changes was unknown
Medication Regimen Management				
Simplify: Maximize doses of one medication before starting another and use combination pills Synchronize: Use medications that can be taken at the same time of day, create 1-time pharmacy pickups	For a patient taking lisinopril for hypertension but who needs an additional agent, prescribe lisinopril combination pill rather than 2 pills	Clinical: In Thom et al,[38] improvement in mean systolic blood pressure (from 137 to 129 mm Hg in intervention group vs 137 to 132 mm Hg in control group; differece in differences, 3 mm Hg) and in LDL-C concentration (from 92 to 84 mg/dL in intervention group vs 93 to 88 mg/dL in control group; difference in differences, 3.2 mg/dL) at 15 mo Adherence: In Castellano et al,[39] proportion of patients who took >80% of their pills improved from 41% in control group to 51% in intervention group at 9 mo	Available, feasible, and generally acceptable to patients	Time required to change regimen and organize single pharmacy pickups may be significant The clinical significance of these changes was unknown
Clinical Pharmacist Consultation				
Use clinical pharmacists when available for (1) education on disease-specific goals for reducing complications (ie, blood pressure goal of 130/80 mm Hg to reduce risk of stroke); (2) monitoring and reporting of disease-specific measurements (ie, home blood pressure or blood glucose) via telephone or in-person follow-up visits; (3) medication adjustment based on home measurements; (4) refill reminder calls May be most helpful for diseases that require frequent medication titration, such as diabetes and hypertension	For a patient with poorly controlled diabetes who needs frequent insulin titration, refer to a clinical pharmacist for disease co-management	Clinical: In Magid et al,[42] improvement in mean systolic blood pressure (from 150 to 137 mm Hg in intervention group vs 144 to 137 mm Hg in control group; difference in differences, 6 mm Hg) at 6 mo Adherence: In Ho et al,[45] proportion of patients who picked up >80% of refills improved from 74% in control group to 89% in intervention group at 1 y	Allows clinicians to share responsibility and draw on other professionals to improve adherence	May not be available in some practices The magnitude of benefit was small and the clinical significance of these changes is unknown
Cognitive Behavioral Therapy				
Refer to a trained specialist for motivational interviewing, planned behavior education, or self-management strategies May be most effective in patients with concurrent psychosocial conditions such as depression	For a patient with HIV and high viral load despite therapy, refer to a psychologist or other trained specialist for motivational interviewing	Clinical: In de Bruin et al,[57] improvement in mean viral load of 10 copies/mL at 15 mo (from 45 copies/mL to 35 copies/mL) Adherence: In Wu et al,[50] proportion of patients classified as adherent (took >88% of pills) improved from 36% in control group to 74% in intervention group at 9 mo	Allows clinicians to share responsibility and draw on other professionals to improve adherence	Most interventions delivered by trained specialists Requires time commitment from patients May not be available in many practices The clinical significance of these changes is unknown

(continued)

Table 2. Summary of Interventions to Improve Adherence (continued)

Description	Example	Maximum Observed Effect	Advantages	Disadvantages
Medication-Taking Reminders				
Refill reminder calls (particularly effective if personal and initiated with new prescriptions) Text or voice reminders from smartphone apps to take medications daily Electronic pill bottles alone (without concurrent reminders) do not improve adherence	For a patient who frequently forgets to pick up medication refills, organize a monthly reminder call from a clinic staff member	Clinical: In Bobrow et al,[67] improvement in mean systolic blood pressure (from 135 to 132 mm Hg in intervention group vs 135 to 134 mm Hg in control group; difference in differences, 2 mm Hg) at 1 y Adherence: In Reese et al,[71] proportion of patients who took doses as scheduled improved from 55% in control group to 88% in intervention group at 6 mo	Some electronic drug monitors can be synchronized to smartphones and require little oversight	Reminders most effective when personal and interactive May not be available in some practices The magnitude of benefit was small and the clinical significance of these changes is unknown
Incentives to Promote Adherence				
Incentives to promote medication-taking behavior (such as money paid to patients per each medication refilled, or money paid to patients or clinicians to achieve goals such as reductions in LDL-C concentration) Reduce co-payments: If 2 medications are equally effective, choose the one with lower patient co-payments	For a patient with a new diagnosis of hypertension and trouble affording medications, choose an antihypertensive with the lowest co-payment (ie, $4 lists available from some retail pharmacies)	Clinical: In Choudhry et al,[72] reduction in the rate of total major vascular events or revascularization from 23% to 21% per 100 person-years at 1 y Adherence: In Choudhry et al,[72] proportion of patients who picked up >80% of refills improved from 39% in control group to 44% in intervention group at 1 y	Generally acceptable to patients	Feasibility and scalability may be a barrier for many practices and health systems Identifying patient co-payments for specific medications may be difficult The clinical significance of these changes is unknown

Abbreviation: LDL-C, low-density lipoprotein cholesterol.

SI conversion factor: To convert LDL-C values to mmol/L, multiply by 0.0259.

Table 3. Summary of Recommendations to Improve Adherence

Recommendations	Method	Details
Clinicians		
Identify patients with suboptimal adherence	Routine history taking (ie, self-report) Incorporate adherence questions into the routine clinical visit (ie, the "fifth vital sign")	Before the clinical encounter, a clinic staff member asks every patient "In the past month, how often did you take your medications as the doctor prescribed?" Possible responses are "nearly all of the time," "most of the time," "half of the time," or "less than half of the time"; an answer of "half of the time" or less should prompt follow-up questions from the clinician
	Monitor for poor disease control	Identify potential markers such as higher-than-expected blood pressure or LDL-C concentration
	Vigilance during high-risk periods	Increased attention to nonadherence at hospital follow-up visits or visits after initiation of medications
Intervene during the clinical visit	Understand reasons for poor adherence	Ask open-ended questions about medication adverse effects, difficulty remembering taking medications, difficulty paying for medications
	Know the specific resources available in the practice, hospital, and/or health system	Availability of nurses for frequent in-person or telephone follow-up, clinical pharmacists available for consultation, medication-taking reminders
	Choose an intervention that is available, feasible, and acceptable to patients (see Table 2 for summary)	Patient education Medication regimen management Clinical pharmacist consultation Cognitive behavioral therapy Medication-taking reminders Incentives to promote adherence
Follow up after the clinical visit	Increase medical contact	More frequent visits (eg, nurse visits) with patients who are suboptimally adherent
Health Systems		
Help clinicians identify patients with suboptimal adherence	Pharmacy claims data	Synchronizing pharmacy claims with electronic health records could help physicians identify patients who have not filled prescriptions
	Electronic drug monitors	Make available for clinicians to give to patients who may be suboptimally adherent
Provide infrastructure for evidence-based interventions	Clinical pharmacists	Allow pharmacists to be available for consultation and follow-up with patients who are suboptimally adherent
	Medical support staff	Ensure adequacy of staff to make frequent follow-up contact possible for patients who are nonadherent

Abbreviation: LDL-C, low-density lipoprotein cholesterol.

members of the clinical team to facilitate the identification of nonadherent patients. Incorporating adherence questions into clinic waiting rooms or rooming procedures by medical assistants are feasible and effective means of identifying patients who may be nonadherent. During the clinical visit, clinicians could then prioritize initiating discussions on adherence and choosing an intervention to improve adherence. Clinicians should also be aware of patient-specific factors, such as socioeconomic status, that may affect the choice of intervention. For example, prescribing a combination pill with a higher co-payment may be a feasible and effective way to improve adherence for one patient, while using 2 generic pills with lower co-payments may be necessary for another. These trade-offs will require a conversation to elicit a patient's barriers to adherence and use of shared decision-making to choose an intervention that is acceptable.

Limitations

This review has several limitations. First, wide heterogeneity in the patient populations, diseases, medications, and outcomes studied may limit the generalizability of conclusions regarding the effectiveness of adherence interventions across all chronic diseases. This heterogeneity similarly limits quantitative comparisons of the categories of interventions based on effect size. Second, none of the studies in this review examined implementation of interventions outside of the clinical trial setting, limiting generalizability to all practices and health systems. Third, studies often did not evaluate clinically important outcomes such as stroke, myocardial infarction, or complications of HIV. Fourth, the clinically practical interventions described here may not completely align with the social-ecological framework for health promotion described in the Discussion,[79] but the framework may help understand the problem of medication nonadherence at a population level.

Conclusions

Adherence can be assessed and improved within the context of usual clinical care, but more intensive and costly interventions that have demonstrated success will require additional investments by health systems.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Edward Livingston, MD, at Edward.livingston@jamanetwork.org or Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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