# Medication Compliance, Adherence, and Persistence: Current Status of Behavioral and Educational Interventions to Improve Outcomes

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## ABSTRACT

**BACKGROUND: Poor adherence and persistence are serious issues in the management of chronic conditions. A mounting body of evidence indicates that decreased medication adherence is associated with increased hospitalizations and total costs of care.**

**OBJECTIVE: To review the predictors of adherence to and persistence with medications and to discuss the intervention strategies that have been used to address adherence in chronic conditions.**

**SUMMARY: Several intervention strategies have been used to address adherence in chronic conditions. These strategies can be grouped into 3 categories: informational, behavioral, and combined strategies. It has been shown that the quality of this research is poor, with wide variability in study design, outcomes, and duration.**

**CONCLUSIONS: Adherence is a multifaceted issue, affected by both behavioral and system barriers. At present, few intervention studies have attempted to identify patient barriers and match patients to interventions designed to affect the identified barriers. No one model is better than all others, but simplification of medication regimens and multifaceted behavioral interventions have shown promise in some research. Additional research, utilizing better study methods to minimize confounding and larger sample sizes, is needed to determine which interventions are effective. Future programs designed to impact adherence should focus on (a) identifying patient-specific adherence barriers, (b) identifying other adherence issues, (c) tailoring interventions to eliminate or reduce barriers, and (d) providing ongoing social support for patients. Once we become better able to tailor effective interventions to meet patient needs rather than offering the same intervention to all patients, we will begin to achieve better outcomes with greater efficiency.**

*J Manag Care Pharm.* 2008;14(6)(suppl S-d):S2-S10



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Poor adherence and persistence are serious issues in the management of chronic conditions. Adherence has been defined as the extent to which a patient's behavior (taking medication, following a diet, modifying habits, or attending clinics) coincides with medical or health advice.[1,2] Persistence, on the other hand, has been defined as the continuation over time with long-term drug therapy prescribed for the management of chronic conditions.[3]

Nonadherence is a multifaceted issue that is linked to both behavioral and system barriers. Behavioral barriers include social support, cognition, and personal beliefs (e.g., regarding health).[4] System barriers include treatment complexity (multiple medications/dosing schedule), system complexity (multiple providers), and cost.[4] As a result, many patients do not take their medications as recommended. For example, a study of Medicaid enrollees aged ≥65 years demonstrated that patients had lipid-lowering medications "on hand" 79% of the time during the first 3 months of treatment.[3] This percentage consistently declined over time to 42% at 10 years. Of these patients, only 60% were considered adherent (had medications on hand >80% of the time) at 3 months, while only 32% were adherent after 10 years.[3] A substantial number of patients fail to even fill a prescription for the second time. Medications with bothersome side effects are more likely to be filled less frequently and are discontinued more often. For diabetes, dyslipidemias, and hypertension, medication nonadherence has been associated with worsened medical treatment outcomes, higher hospitalization rates, and/or increased health care costs.[5,6]

### Impact of Adherence on Health and Total Health Care Costs

A mounting body of evidence demonstrates that decreased medication adherence is associated with increased hospitalization rates and total costs of care.[6,7] A retrospective cohort study of patients continuously enrolled in medical and prescription benefit plans sought to evaluate the impact of medication adherence, measured by using the medication possession ratio (MPR), on health care utilization and cost for 4 major disease states: diabetes, congestive heart failure (CHF), dyslipidemias, and hypertension.[6] Hospitalization risk, defined as the probability of ≥1 hospitalizations during a 12-month period, was one of the primary outcomes of the analysis. In this cohort, hospitalization risk decreased for patients with diabetes and hypertension as the MPR increased. However, the proportion of patients requiring hospitalization was inconsistently related to MPR for patients with CHF and dyslipidemias. Costs associated with patient care were more difficult to decipher. Patients who were more adherent to their medication therapies incurred higher medication costs, as would be expected, for all conditions (diabetes, CHF, dyslipidemia, hypertension). Total disease-related health care costs were lower for adherent patients with diabetes compared with

nonadherent patients ($4,570 for 80%-100% MPR vs. $8,867 for 0%-19% MPR). Similarly, adherent patients with dyslipidemia had lower total disease-related health care costs than did nonadherent patients ($3,924 for 80%-100% MPR vs. $6,888 for 0%-19% MPR). No clear association was found between medication adherence and disease-related health care costs for patients with hypertension or CHF.

In a 5-year longitudinal study of 775 patients enrolled in a Medicare health maintenance organization in North Carolina, significant predictors of higher total annual health care costs in patients with diabetes were identified.[7] These predictors included a lower MPR; a 10% increase in antidiabetic MPR was associated with an 8.6% statistically significant decrease in total annual health care costs ($P<0.001$). Predictors of higher health care costs included having more comorbidities, using more oral diabetic agents, filling a greater number of prescriptions, and incurring more emergency room visits during the previous year.

However, the possibility exists that patients who naturally adhere to therapy are also adherent to other healthy lifestyles. In a meta-analysis by Simpson et al. of 21 studies comprising 46,847 total participants (including 19,633 participants assigned to placebo arms), good adherence to either beneficial drug therapy (odds ratio [OR]=0.55; 95% confidence interval [CI]=0.49-0.62) or placebo (OR=0.56; 95% CI=0.43-0.74) was associated with lower mortality rates.[8] Good adherence to harmful drug therapy was associated with increased mortality risk (OR=2.90; 95% CI=1.04-8.11). These findings supported the concept of the "healthy adherer" phenomenon.

More recently, a population-based, observational, longitudinal study of 31,455 elderly acute myocardial infarction survivors in Ontario sought to verify whether the healthy adherer phenomenon exists outside of clinical trials, where placebo and Hawthorne effects may confound findings.[9] In this study, all patients filled a prescription for statins, beta-blockers, or calcium-channel blockers. Patients receiving calcium-channel blockers served as the control, given the absence of clinical trial-proven survival benefit. For statins, the risk of mortality was greater for low-adherence than for high-adherence patients (deaths in 261/1,071 [24%] patients vs. 2,310/14,345 [16%] patients; adjusted hazard ratio [HR]=1.25; 95% CI=1.09-1.42; $P=0.001$). Death rates for intermediate adherers fell between those of the other groups (deaths in 472/2,407 [20%] patients; adjusted HR=1.12; 95% CI=1.01-1.25; $P=0.03$). A "similar but less pronounced" association between adherence and mortality was observed for individuals receiving beta-blockers. Mortality was not associated with adherence to calcium-channel blockers, suggesting that there was no survival advantage due to hypothesized alternative healthy behaviors in adherent individuals. Adherence to life-saving medications is the likely reason for increased life expectancy in the statin- and beta-blocker–treated individuals. Although this retrospective study does not completely dispel the possibility that the healthy adherer phenomenon exists (especially given that contradictory evidence exists), it does suggest that adherence to life-preserving medications improves survival beyond what might be expected from other healthy behaviors associated with highly adherent individuals.

In summary, improved adherence leads to better patient outcomes, higher medication costs, and mixed effects on total health care costs, most likely depending on the condition being treated.

## Predictors of Poor Adherence and Persistence

Patient adherence to therapy depends on a number of behavioral and system factors. Identified risk factors for poor adherence include living alone, low socioeconomic status, higher number of medications taken, higher medication costs, lack of prescription drug coverage, higher number of physicians caring for the patient, depression, cognitive impairment, treatment of asymptomatic disease, presence of side effects to medications, poor provider-patient relationship, complex treatment regimens, and financial issues.[4,10-13] Common modifiable predictors of poor adherence include treatment complexity, polypharmacy, cost, duration of medication regimen (for acute conditions), and multiple providers.[11-13]

Patient perceptions of the severity of their condition have also been associated with medication-taking behavior. In a recent meta-analysis, nonadherence was shown to be >1.5 times higher among individuals who did not perceive their disease as severe or as a threat.[14] Among conditions of greater seriousness, worsened adherence was associated with objectively poorer health. Better patient adherence was associated with objectively poorer health only for those patients experiencing disease conditions that were lower in seriousness.[14]

In a survey of women prescribed oral bisphosphonates, concerns about medication safety or effectiveness were strongly associated with poor adherence.[15] Forgetting, losing, or running out of their medication were the most common reasons (37.4% of respondents) for incomplete adherence in a survey of adults taking oral psychotropic medications.[16]

Patient demographics and comorbidities may also play a role in adherence. Predictors of poor long-term persistence with statin use in a cohort of 34,501 enrollees aged ≥65 years included nonwhite race, lower income, older age, less cardiovascular morbidity at initiation of therapy, depression, dementia, and occurrence of coronary heart disease events after starting treatment.[3]

## Cost-Sharing Mechanisms and Their Impact on Medication Adherence

Rising health care expenditures have led insurance plans to try various measures of cost control. One example of this effort is the use of tiered benefit designs. Tiered benefits are intended to decrease health plan costs by increasing generic utilization, decreasing brand utilization, and shifting some costs to plan beneficiaries.[17] While tiered benefit designs have been shown

to decrease health plan costs, cost-sharing has also been associated with reductions in medication utilization.[18] A number of studies have demonstrated that cost-sharing is associated with reduced use of essential and nonessential drugs.[18-24] These studies varied considerably in their results, which was likely due to methodology, populations studied, and amount of cost-sharing change examined.[18] The degree to which medication use may be impacted appears to depend on the patient's ability to pay for medications as well as the condition being treated, which may also account for some of the observed differences in the study findings.[18,20] For example, doubling of the copayment was predicted to reduce days of drug supplied by 16% for generics and 21% for branded medications in a simulation model based on data from 30 employers and 52 health plans.[20] Predicted use of medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) and antihistamines, which are used for symptomatic relief, was most affected by altered copayments, whereas patients diagnosed with chronic conditions were predicted to reduce their medication use to a lesser extent.[20]

Also, use of medications with close over-the-counter substitutes, including NSAIDs, antihistamines, and antiulcerants, was particularly likely to be associated with higher copayment levels, suggesting that substitution with less costly and potentially less effective medications may be common when cost-sharing is implemented. For patients with chronic illnesses who were receiving ongoing care, the association of copayments with reduced utilization was not as strong as for those without a documented indication or with more acute conditions.[20] The impact of cost-sharing on adherence appears be greater for low-income groups than for those with higher incomes.[18] In employer-based insurance groups, some studies have shown a negative association between cost-sharing and adherence or persistence,[21,23] while quasi-experimental studies have not detected an impact on adherence.[25,26] Two studies in commercially insured populations found that modest changes in cost-sharing (up to $10 in one study, $12 in another) had no detectable impact on adherence, while larger changes (>$10 in one study, $23 in another) were associated with a negative impact on adherence.[27,28] In short, the impact of cost-sharing on adherence is a complicated issue. Readers are referred to existing reviews for more comprehensive discussions of this topic.[17,29,30]

**TABLE** Informational Intervention Trials

| First Author/Year | Condition | Model | Frequency |
|---|---|---|---|
| **Canto de Cetina/2001**[33] | Injectable contraception (I=175, C=175) | Not stated/"structured" counseling | Structured counseling program before each injection every 3 months |
| **Cote/2001**[34] | Asthma (I=33, C=30) | PRECEDE Model: addresses beliefs, attitudes, knowledge, and social support | Structured education program, repeated at 6 months |
| **Gallefoss/1999**[35,36] | Asthma (I=39, C=39)<br>COPD (I=31, C=31) | Not stated/multidisciplinary | Educational booklet, 2×2-hour group sessions, 1 or 2 individual sessions (40 minutes) |
| **Hill/2001**[37] | Rheumatoid arthritis (I=51, C=49) | Self efficacy | Individual education, 7×30-minute sessions |
| **Laporte/2003**[38] | Thromboembolic disease (I=43, C=43) | Not stated | Intensive. Daily visits while in hospital, daily tests on education |
| **Levy/2000**[39] | Asthma I=103, C=108 | Not stated/individual education by nurse | Initial 1-hour session, then 2×30-minute sessions 6 weeks apart |
| **Morice/2001**[40] | Asthma (I=40, C=40) | Not stated/individual education by nurse | Educational booklet, 2×30-minute educational sessions, self-management plan |
| **Peterson/2004**[41] | Dyslipidemia (I=45, C=49) | Not stated/home visits by pharmacist | Monthly×6 months |
| **Pradier/2003**[42] | HIV (I=124, C=122) | Individual session with cognitive, emotional, social, and behavioral aspects | 3×45- to 60-minute sessions |
| **Rawlings/2003**[43] | HIV (I=96, C=99) | Not stated/"Tools for Health and Empowerment" course featuring interactive small group sessions provided by trained health care professionals | Weekly×4 weeks, duration of program not provided. |
| **Schaffer/2004**[44] | Asthma (I=33 [3 groups], C=13) | Protection Motivation Theory/audio tape and/or booklet (3 intervention groups) | Patient review of written or audio materials (approximately 30-60 minutes) |
| **Van Es/2001**[45] | Asthma (I=58, C=54) | ASE | Intensive education, 12 months. Discuss self-management plan with physician, individual education by nurse, 4 x 30-minute sessions with nurse, 3 x 90-minute sessions with group |

*ASE=Attitude, social influence, efficacy; C=control group; COPD=chronic obstructive pulmonary disease; HIV=human immunodeficiency virus; I=intervention group; PRECEDE=Predisposing, Reinforcing, and Enabling Constructs in Educational Diagnosis and Evaluation.*

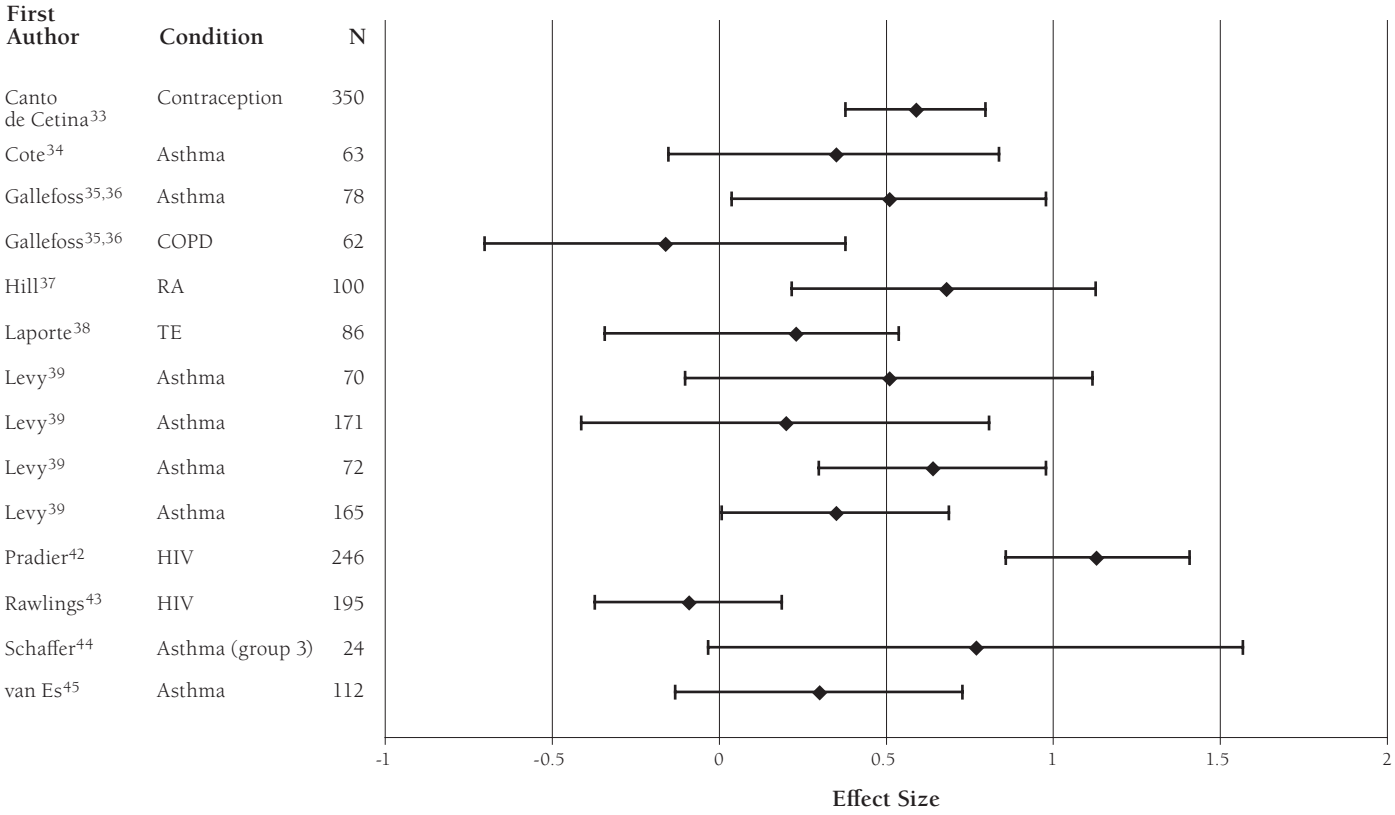
## Intervention Strategies

Several intervention strategies have been used to address adherence in chronic conditions. Unfortunately, interpretation of these study findings is difficult due to wide variability in study design, outcomes, and duration.[31] In the following sections, we will summarize some of the more rigorous studies evaluating adherence interventions. Studies selected for this review were those identified in the systematic review by Kripalani et al.[32] Articles were selected by Kripalani et al. if they reported a randomized controlled trial with unconfounded interventions specifically intended to enhance medication adherence. Studies had to report adherence and at least 1 clinical outcome. Effect size (using Cohen's d) and the 95% CI were presented for all studies. These strategies can be grouped into 3 categories: informational, behavioral, and combined strategies. The following sections will review the effectiveness of each strategy.

## Informational Interventions Through Educational Processes

Informational interventions have been described as cognitive strategies designed to educate and motivate patients by instructional means. The premise for this concept is that patients who understand their condition and its treatment will be more informed, have more control, and be more likely to comply. Studies of educational interventions given to patients for improving adherence are summarized in the Table.[33-45] Changes in adherence are presented in Figure 1, and the study's primary clinical outcome is presented in Figure 2. Effect sizes represent the difference in effect between a study's intervention and control groups divided by the standard deviation of the difference. An effect size of <0.2 is considered very small, 0.2-0.5 is small, 0.5-0.8 is medium, and >0.8 is large. Differences in the models and intensities of education are also listed in the table. Interestingly, no clear association was found between intervention intensity

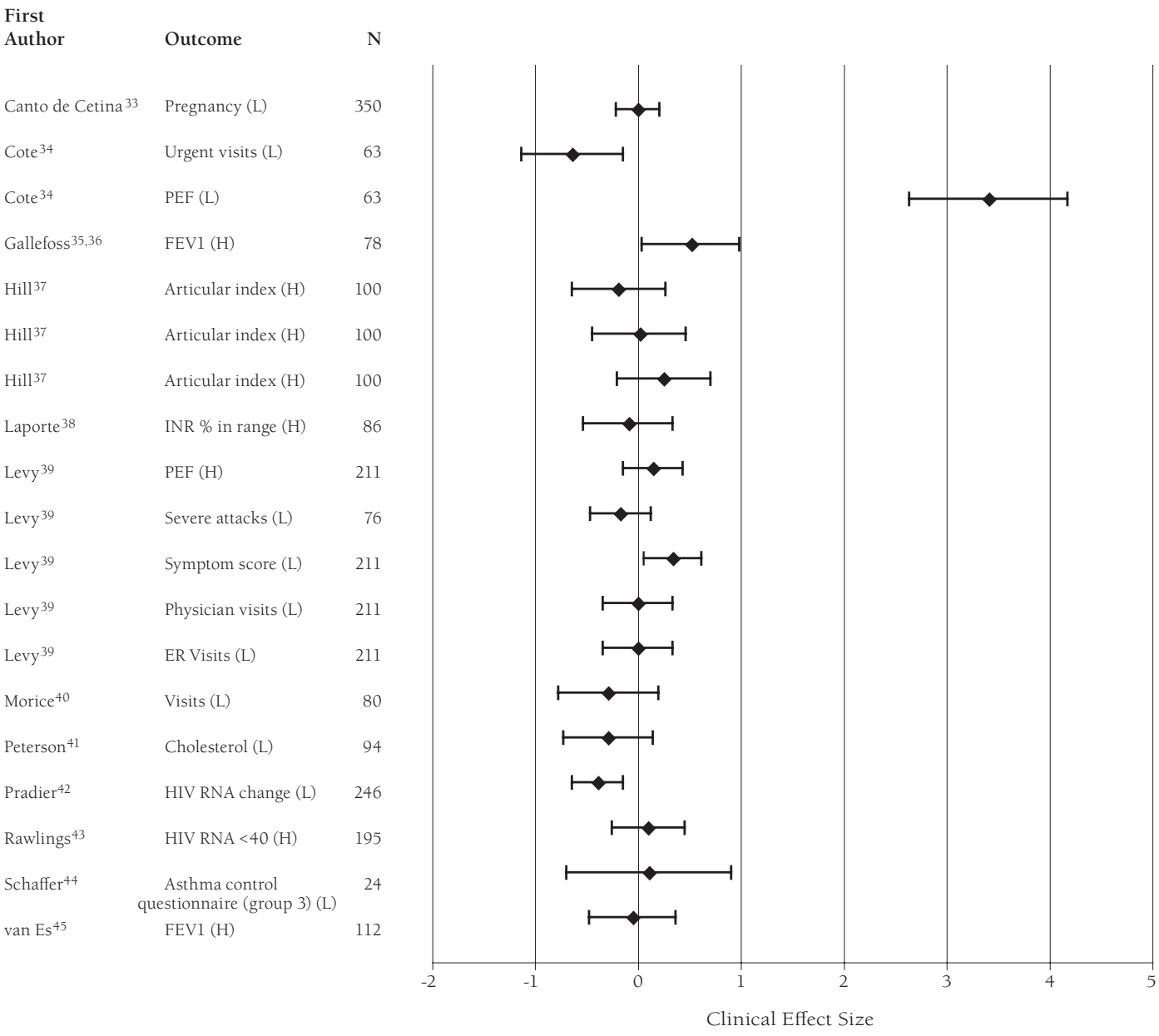
**FIGURE 1** *Informational Interventions: Effect Sizes[a] for Medication Adherence Measures*




[a]*Effect size was calculated using Cohen's d by Kripalani et al.[32] An effect size of <0.2 is considered very small, 0.2-0.5 is small, 0.5-0.8 is medium, and >0.8 is large. Effect sizes were not reported for adherence measures in Morice and Wrench[40] and Peterson et al.[41]*

*COPD=chronic obstructive pulmonary disease; HIV=human immunodeficiency virus; RA=rheumatoid arthritis; TE=thromboembolic disease.*

**FIGURE 2** *Informational Interventions: Effect Sizes[a] for Clinical Measures*




[a]*Effect size was calculated using Cohen's d by Kripalani et al.[32] An effect size of <0.2 is considered very small, 0.2-0.5 is small, 0.5-0.8 is medium, and >0.8 is large. ER=emergency room; FEV1=forced expiratory volume in 1 second; H=higher is better; HIV=human immunodeficiency virus; INR=international normalized ratio; L=lower is better; PEF=peak expiratory flow; RNA=ribonucleic acid.*

and effect size; high-intensity interventions did not necessarily result in better outcomes. Outcomes of the educational programs may be more dependent on the willingness and ability of the patient to accept and use the information being provided than on the intensity of the program. However, a link has been demonstrated between the time spent with a care provider and improved hemoglobin A1c (but not necessarily improved adherence to medications) in patients with diabetes.[46]

Of 12 informational interventions studied by Kripalani et al., one-half (6 studies) reported a significant improvement in at least

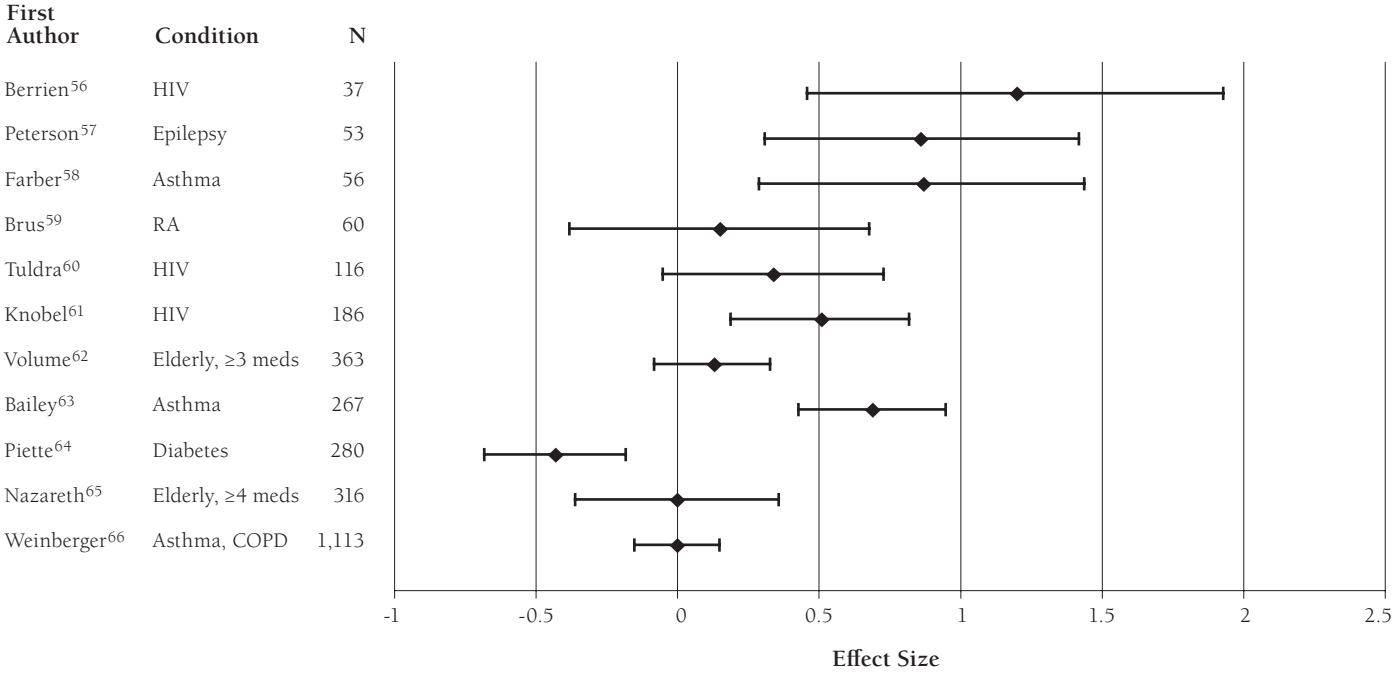
1 adherence measure; however, only 4 of the 12 interventions were associated with any improvement in clinical outcome. Of the 2 informational intervention studies that were associated with consistently improved clinical outcomes, significant improvement in medication adherence was noted in one study but not the other.[32] For example, the Gallefoss et al. study did show a significant improvement in forced expiratory volume (FEV1) at 12 months in asthma patients (+112 ± 386 mL vs. -83 ± 383 mL; $P<0.05$), but no improvement was seen in FEV1 in the chronic obstructive pulmonary disease group.[35,36] In the Cote et al. study, there was a significant difference in the number of urgent visits for asthma exacerbations (9 vs. 34 in intervention and control groups, respectively; $P=0.03$).[34] In these studies, there was no clear evidence to demonstrate that improvement in adherence results in improvement in clinical effectiveness with educational interventions, although study limitations, such as insufficient sample size, may have prevented the identification of such an association.

## Behavioral Interventions

Behavioral interventions are designed to influence behavior through shaping, reminding (cues), or rewarding desired behavior (reinforcement).[32] Examples of these methods include teaching the patient skill building, using reminder methods (pillboxes, calendars, packaging changes), simplifying the dosing schedule (i.e., reducing its behavioral demands), and using rewards and reinforcement (e.g., assessment of adherence with feedback to the patient).

Three studies have shown that reduction in the number of tablets used increases adherence in patients with hypertension,[47,48] hyperlipidemia, and coronary artery disease.[49] Once-daily dosing results in superior adherence compared with twice-daily dosing,[47,48] and a twice-daily schedule shows better adherence than 4-times-daily dosing.[49] Again, clinical outcomes were not impacted in most studies. Only Brown et al., who compared controlled-release niacin twice daily to regular niacin 4 times daily, demonstrated a statistically significant improvement in the clinical outcome of target cholesterol levels.[49]

**FIGURE 3** Mixed Interventions: Effect Sizes[a] for Medication Adherence Measures




[a]*Effect size was calculated using Cohen's d by Kripalani et al.[32] An effect size of <0.2 is considered very small, 0.2-0.5 is small, 0.5-0.8 is medium, and >0.8 is large. COPD=chronic obstructive pulmonary disease; HIV=human immunodeficiency virus; meds=unique medications; RA=rheumatoid arthritis.*

Special packaging or pill boxes have also been evaluated as a method of improving adherence. In patients with hypertension, Becker found that special packaging had no significant impact on adherence or clinical outcomes.[50] A difference in blood pressure of 3.5 mm Hg was observed, but this difference was not statistically significant. While patients found that packaging may help them remember to take their medications, the packaging was more difficult to use.

Reminder systems have been shown to have a more significant impact on adherence and clinical outcomes. One study showed that weekly phone calls for 6 months improved adherence (18% vs. 12%, $P$=0.03), resulting in a nonsignificant reduction in systolic blood pressure and a significant reduction in diastolic blood pressure (5.2% vs. 0.8% reduction; $P$=0.02).[51] Another study showed that 3 telephone calls to patients in 4 months improved adherence with significant reductions in low-density lipoprotein cholesterol (LDL-C).[52] Mean adherence rates were 84% in the control group and 93% in the intervention group ($P$<0.001). The proportion of patients with LDL-C values at goal was 44% in the intervention group compared with just 23% in the control group ($P$<0.005).

Increased patient involvement and self-care models have shown mixed results. One study that used self-monitoring of pills and blood pressure, a tailored medication schedule, home visits by a research assistant, and rewards showed a moderate improvement in adherence (65.8% vs. 43.2%, $P$=0.02),[53] while another study that used self-monitoring of blood pressure and monthly home visits by a research assistant showed no change in adherence.[54] No improvements in clinical outcomes were detected in either study, although both studies were limited by small sample sizes. In a study assessing a cognitive behavioral therapy intervention, 3-25 sessions during a 1-year period in 32 patients had no impact on medication adherence or HIV viral load.[55]

### Mixed Interventions

Mixed interventions include those that have features of 2 or 3 of the preceding categories. In a recent meta-analysis of chronic conditions, many of the smaller studies showed an improvement in adherence, while the larger studies showed no improvement (Figure 3).[32,56-66] Five of 13 studies that employed informational and behavioral elements in the review showed improvement in all adherence measures.[57,58,61,63,64] While none of the interventions impacted all measured clinical outcomes, at least 1 clinical outcome was impacted in 4 of the 13 studies.[61,63,64,66] Two additional studies employing social support interventions were evaluated.[67,68] One of these studies demonstrated an impact on adherence[68] but no significant impact on clinical outcomes. No consistent relationship was observed between disease state and success of the intervention. These mixed findings are difficult to explain because studies with small sample sizes were able to show significant results while larger studies often did not. Possible reasons for this outcome are that (a) the smaller studies used more complicated interventions that may have produced a greater effect and (b) a publication bias may exist in which small studies showing positive results are more likely to be published than small studies showing negative findings. Larger, well-designed studies are less susceptible to publication bias because they are published even when the results show no improvement in outcomes.

## Discussion

According to Kripalani et al., some types of interventions were more likely to improve adherence.[32] Interventions that simplified the dosing regimen consistently increased adherence. Also, complex programs that utilized multiple interventions delivered over a longer period of time appeared more likely to achieve better outcomes. It is likely that these more complex interventions are effective because they address a greater number of the potential barriers impacting a patient's ability to adhere to therapy and provide reinforcement over time. However, complex interventions are more difficult to duplicate outside of an academic setting where sufficient resources may not exist to fully replicate the intervention. Complex interventions make it difficult to determine which aspects of the intervention are responsible for the observed outcomes. Also, complex programs may not be cost-effective or practical. Costs of running an interventional program are considered true expenditures, while cost offsets returned by the program (e.g., improved patient health, reduced hospitalizations) are difficult to calculate or estimate because they are included with other health care costs. Thus, it is often difficult to justify intervention programs to a health plan.

To determine which interventions are effective, additional research is needed using better trial designs to minimize crossover bias and other common methodological issues. Studies should attempt to separate the control and intervention groups by using cluster randomization techniques whenever possible. Studies should have sufficient sample sizes to detect differences in clinical outcomes. Ideally, conducting studies in real-world settings is preferred so that the intervention can be easily replicated. However, there are considerable challenges when conducting studies outside of the more controlled (and stable) academic center setting.[69]

Future assessments of adherence interventions must determine the effects of individual intervention components by studying each independently before combining their effective components. However, because adherence is multifaceted, a single component may produce only small changes in outcomes by itself, making demonstration of the benefits difficult. We also need to determine the best methods of delivering the intervention to patients. How does varying the amount of time that a clinician spends with a patient change the outcome? Do certain types of interventions require more patient contact to be effective? Is it better to spend more time with a patient early in the intervention? The long-term effects of some interventions may wane without constant rein-

forcement.[70] While optimal programs may be very time intensive and attack adherence issues with multiple mechanisms, effective programs must also strive to be efficient if they are to be adopted in nonresearch settings.

## Conclusion

A significant proportion of patients fail to adhere to recommended therapies, with adherence declining over time. Even effective interventions have had a limited impact on changing adherence. Interventions that show promise are (a) simplification of a patient's medication regimen, which has consistently been shown to improve adherence, and (b) multifaceted behavioral interventions, which are sometimes effective but may be difficult to reproduce. Future programs designed to impact adherence should focus on (a) identifying patient-specific adherence barriers, (b) identifying other adherence issues, (c) tailoring interventions to eliminate or reduce barriers, and (d) providing ongoing social support for patients. Once we become better able to tailor effective interventions to meet patient needs rather than offering the same blanket intervention to all patients, we will begin to achieve better outcomes with greater efficiency.

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