Interventions to Enhance Medication Adherence in Chronic Medical Conditions

A Systematic Review

Sunil Kripalani, MD, MSc; Xiaomei Yao, MD; R. Brian Haynes, MD, PhD

Background: Approximately 20% to 50% of patients are not adherent to medical therapy. This review was performed to summarize, categorize, and estimate the effect size (ES) of interventions to improve medication adherence in chronic medical conditions.

Methods: Randomized controlled trials published from January 1967 to September 2004 were eligible if they described 1 or more unconfounded interventions intended to enhance adherence with self-administered medications in the treatment of chronic medical conditions. Trials that reported at least 1 measure of medication adherence and 1 clinical outcome, with at least 80% follow-up during 6 months, were included. Study characteristics and results for adherence and clinical outcomes were extracted. In addition, ES was calculated for each outcome.

Results: Among 37 eligible trials (including 12 informational, 10 behavioral, and 15 combined informational, behavioral, and/or social investigations), 20 studies reported a significant improvement in at least 1 adherence measure. Adherence increased most consistently with behavioral interventions that reduced dosing demands (3 of 3 studies, large ES [0.89-1.20]) and those involving monitoring and feedback (3 of 4 studies, small to large ES [0.27-0.81]). Adherence also improved in 6 multisession informational trials (small to large ES [0.35-1.13]) and 8 combined interventions (small to large ES [absolute value, 0.43-1.20]). Eleven studies (4 informational, 3 behavioral, and 4 combined) demonstrated improvement in at least 1 clinical outcome, but effects were variable (very small to large ES [0.17-3.41]) and not consistently related to changes in adherence.

Conclusion: Several types of interventions are effective in improving medication adherence in chronic medical conditions, but few significantly affected clinical outcomes.

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Author Affiliations: Division of General Medicine, Department of Internal Medicine, Emory University School of Medicine, Atlanta, Ga (Dr Kripalani); and Department of Clinical Epidemiology and Biostatistics (Drs Yao and Haynes) and Department of Medicine (Dr Haynes), McMaster University, Hamilton, Ontario.

An estimated 20% to 50% of patients do not take their medications as prescribed and are said to be nonadherent or noncompliant with therapy. In the setting of chronic medical conditions such as hypertension and hypercholesterolemia, medication nonadherence leads to worse medical treatment outcomes, higher hospitalization rates, and increased health care costs. Because of this, adherence has been called “the key mediator between medical practice and patient outcomes.”

Researchers have tested a variety of interventions to improve patient adherence, ranging from simple adjustments in the medication regimen to complex multidisciplinary interventions that address health system barriers and communication between patients and health care professionals. However, the overall quality of the literature is poor, with wide variability in study design, including patient population, outcome measure, and duration of follow-up. It is desirable to draw recommendations from a smaller set of high-quality studies.

In a recent review for the Cochrane Database, several simple interventions appeared to improve adherence with short-term regimens, such as a course of antibiotics. However, interventions to improve medication use for chronic conditions appeared less effective overall and were often multifaceted, making it more difficult to synthesize published evaluations. In this article, we extend the findings of the Cochrane review by providing a more detailed examination of interventions to improve adherence in chronic medical conditions. We offer a framework for categorizing these interventions and report their relative impact using a standardized measure of effect size (ES). The goal of this review is to help physicians better understand the strengths and limitations of tested interventions for improving long-term medication use and identify those that are most successful.
METHODS

DATA SOURCES

Electronic searches of the published literature from January 1967 to September 2004 were conducted through MEDLINE, CINAHL, PsycINFO, SOCIOPHILE, International Pharmaceutical Abstracts, EMBASE, and The Cochrane Library, without language restriction. The exact search strategy varied across databases and generally included terms for adherence (eg, compliance, noncompliance, adherence, dropouts, treatment refusal), medication use (eg, medication, medicine, drug, treatment, regimen, pharmacotherapy), and clinical trial design (eg, clinical trial, intervention, outcome, randomized, control). A full description of the search strategy is provided elsewhere.12

STUDY SELECTION

Reviewers screened citation titles, index terms, and abstracts (if available) to identify potentially relevant articles, which were retrieved for full-text review. Two reviewers independently assessed the articles for possible inclusion. Differences in assessment were resolved by discussion or with assistance from a third reviewer.

Articles were selected if they reported a randomized controlled trial that described 1 or more unconfounded interventions intended to enhance adherence with self-administered medications used in the treatment of chronic medical conditions. Confounding was judged to be present if study groups were treated unequally except for the intervention intended to enhance adherence (eg, patients in the intervention group received not only more encouragement to comply but also a different medication or dose than those in the control group). Included studies were required to report at least 1 measure of medication adherence and 1 clinical outcome, with at least 80% follow-up of participants during 6 months if the study results were initially positive. Studies with negative results and less than 6 months of follow-up were included because individual failure was unlikely to be followed by success. Studies of short-term regimens were included in the Cochrane review11 but excluded from the present analysis to permit a focus on chronic medical conditions, for which adherence is a greater concern. Trials that pertained to psychiatric disorders were excluded because adherence is generally lower in patients with psychiatric disorders and unique challenges may also be present, potentially limiting the generalizability of interventions tested in that context.13

DATA EXTRACTION

For each eligible study, 1 reviewer extracted features of the patient population, study design, interventions, and control, as well as results for adherence and clinical outcomes. When multiple time points were provided, data were extracted for the longest period of follow-up, provided follow-up remained at least 80%. Each extraction was confirmed by at least 1 other reviewer. Other articles on the same trial were retrieved, and authors were contacted as needed for additional details or verification of reported analyses.

DATA SYNTHESIS

The eligible studies differed substantially in patient population, intervention, adherence measure, and clinical outcome measure, making a pooling of results inappropriate. Instead, studies were grouped by intervention type, using a taxonomy developed from other sources.8,9,14,15 Informational interventions described cognitive strategies designed primarily to educate and motivate patients by instructional means, based on the concept that patients who understand their condition and its treatment will be more informed, empowered, and likely to comply. Informational sessions conducted individually or in a group setting, as well as didactic and interactive approaches, were included. Examples of informational interventions are face-to-face oral, telephone, written, or audiovisual education; didactic group class; and mailed instructional material (not including reminders or prompts to comply). Behavioral interventions were strategies designed to influence behavior through shaping, reminding (cues), or rewarding desired behavior (reinforcement). Examples include skill building by a health care professional; pillboxes, calendars, a change in packaging, or other steps intended to remind the patient; changes in dosage schedule to simplify the regimen or tailor the regimen to the patient's daily routine (ie, reduce its behavioral demands); and rewards and reinforcement (eg, assessment of adherence with feedback to the patient). Family and social interventions involved social support strategies, whether provided by family or another group. Examples are support groups and family counseling. Group sessions that were primarily didactic or informational, rather than supportive, were categorized as informational. Combined interventions included features of 2 or 3 of the preceding categories. Each included study was classified by 1 author using these categories, descriptors, and examples. This classification was reviewed by at least 1 other author, and disagreements were resolved by consensus.

For each outcome, an ES (Cohen d) with 95% confidence interval was calculated from information provided in the article or obtained from the authors. The ESs compare the difference in effect between study groups, divided by the standard deviation of this difference, resulting in standard deviation units.16 This measure is independent of the method of measurement used, thus permitting comparison of different interventions across studies. In this way, ES provides more information than a simple test of significance comparing outcomes in intervention and control groups. The ES can be positive or negative, depending on the effect of the treatment on the particular outcome measure. If the study results are statistically significant, then the ES is generally significant as well.

We calculated ESs according to established methods.16,17 For studies that provided range instead of a standard deviation, we converted range to standard deviation.18 The absolute value of each statistically significant ES was categorized as very small (<0.20), small (0.20 to <0.50), medium (0.50 to <0.80), or large (>0.80).18 We calculated ESs between each intervention and control group. Some studies had more than 2 arms and provided only an overall test of significance comparing results across experimental groups. In these cases, the significance of the ES for intervention-control pairs may have differed from the overall significance of results. Also, if study authors did not specify the number of patients involved in the final analysis, we used the baseline sample size of each group to calculate the ES. Calculating the ES in this way, analogous to an intention-to-treat analysis, may underestimate the true effect of the intervention.

RESULTS

The electronic searches returned 13,061 citations (including 458 review articles), 955 of which were judged to merit full-text review. A total of 38 articles describing 37 randomized controlled trials met all inclusion criteria, including 2 articles from the same trial.19,20 Among the in-
cluded studies, 13 reported on 12 informational interventions, 19-31 10 on behavioral interventions, 32-41 and 15 on combined interventions. None described purely family or social interventions (Figure).

Most studies reported a single measure of adherence. However, the choice of measure varied widely, from self-report scales to more objective measures obtained by auditing refill rates, performing pill counts, and assessing the timing of prescription bottle opening by Medication Event Monitoring System caps. Approximately half of the studies reported a single clinical outcome, which also varied greatly, depending on the patient population.

The ES could be calculated in 30 studies for adherence outcomes and in 30 studies for clinical outcomes. Most studies (71% for adherence and 100% for clinical outcomes) that did not provide enough information to calculate the ES were not statistically significant, which illustrated a form of reporting bias.

INFORMATIONAL INTERVENTIONS

The studies of informational interventions each compared intensive education to limited education or usual care (Table 1). Sample size varied from 46 to 350. The interventions ranged in duration from a single session of less than 1 hour to several hours over many sessions. Counseling was provided by a physician, nurse, health educator, or pharmacist. Both individual and group sessions were described, sometimes in combination, and they were often accompanied by written materials.

Half (6 of 12) of these studies reported a significant increase in at least 1 measure of adherence. 19-21,23,25,26,30 However, 3 of these 6 trials had mixed results. Gallefoss et al19,20 reported an improvement among only patients with asthma not those with chronic obstructive pulmonary disease. Levy et al23 demonstrated improvement in adherence only for severe, not mild, asthma attacks. In the study by Schaffer and Tian30 of 3 educational strategies, 2 were effective.

Among the 10 studies for which an ES for adherence outcomes could be calculated, 19,25,28-31 a large ES was observed only in a trial conducted by Pradier et al28 of intensive, multisession counseling for human immunodeficiency virus (HIV) treatment adherence (ES, 1.13 for self-reported adherence). Four other studies 19,21,23,25 that provided counseling over multiple sessions had a small to medium ES (range, 0.35-0.68), and the remainder were not significant.

Most informational interventions (8 of 12) did not improve clinical outcomes. Of the 4 studies with at least 1 positive clinical result, 2 had a small ES (Pradier et al28: ES, −0.39 for HIV RNA level; Levy et al32: ES, 0.34 for asthma symptom scores). The other 2 trials had medium to large ESs (Gallefoss et al19,20: ES, 0.52 for forced expiratory volume in 1 second in patients with asthma; Cote et al22: ES, −0.64 for urgent asthma-related visits and 3.41 for peak expiratory flow). Each of these 4 studies provided fairly intensive counseling with reinforcement over time. Only the interventions used by Cote et al22 and Pradier et al28 consistently led to better clinical outcomes, despite the study by Cote et al having no effect on adherence owing to a high rate of adherence in the control group (97%). Gallefoss et al19,20 again saw improvement only among the asthma subgroup, and Levy et al32 had mixed results based on the clinical outcome measure.

BEHAVIORAL INTERVENTIONS

The sample size of the behavioral studies ranged from 27 to 497 (Table 2). The most common and effective forms of behavioral intervention were dosage simplification12,34,36 and repeated assessment of medication use with feedback.35,37-39 Other trials tested specialized packaging,33 directly observed therapy,40 and cognitive behavior therapy,41 but none of these techniques significantly affected adherence or clinical outcomes.

All 3 trials of dosage simplification demonstrated an improvement in adherence, whether switching from 2 doses to 1 dose per day or from 4 to 2.32,34,36 The ESs that could be calculated were large (range, 0.89-1.20).34,36 The impact on clinical outcomes was mixed. Brown et al34 found a significantly higher percentage of patients reached their low-density lipoprotein cholesterol goal when prescribed extended-release niacin compared with the short-acting form (medium ES of 0.66). However, the study by Baird et al32 of once-daily metoprolol demonstrated no
<table>
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<tr>
<th>Source</th>
<th>Population and Sample Sizes</th>
<th>Intervention/Control</th>
<th>Adherence Measures and Results, %</th>
<th>ES (95% CI) for Adherence</th>
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<tr>
<td>Canto de Cetina et al.23</td>
<td>I = 175, C = 175</td>
<td>I: Structured pretreatment counseling on DMPPA with audiovisual materials, including mode of action, expected benefits, and side effects (emphasized no harm to health), reinforced at each follow-up visit. C: Routine information on expected side effects.</td>
<td>Continued DMPPA (clinically significant, 12 mo): I = 82.9, C = 56.6, Δ = 26.3, P&lt;.05</td>
<td>Medium, 0.59 (0.38 to 0.80)</td>
<td>Pregnancy rate: I = 0, C = 0, Δ = 0, P = NS</td>
<td>None, 0 (-0.21 to 0.21)</td>
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<td>Cote et al.22,2001</td>
<td>Asthma, I = 33, C = 30</td>
<td>I: Structured education: limited education plus structured educational program (PRECEDE model), addressed beliefs, attitudes, knowledge, and social support, reinforcement at 6-mo visit. C: Limited education on inhaler technique and self-management plan based on PEF.</td>
<td>Had prescription for inhaled steroid inhaler (self-report, 12 mo): I = 100, C = 97, Δ = 3, P = .70</td>
<td>None, 0.35 (-0.15 to 0.84)</td>
<td>(1) Urgent visits for asthmatic exacerbation (6-12 mo): I = 8, C = 34, Δ = 26, P = .03; (2) PEF (mean ± SEM, 12 mo): I = 404 ± 25, L/min, C = 349 ± 19 L/min, Δ = 75 L/min, P = .03</td>
<td>(1) Medium, −0.64 (−1.13 to −0.14); (2) large, 3.41 (2.64 to 4.18)</td>
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<td>Gallefoss et al.19,20,1999</td>
<td>Asthma (I = 39, C = 39) and COPD (I = 31, C = 31)</td>
<td>I: Educational booklet, group sessions (2-3-h sessions) by physician and pharmacist, 1 or 2 individual sessions (40 min) from both a nurse and a physiotherapist, self-management plan. C: Usual care.</td>
<td>Received &gt;75% of prescribed doses of inhaled steroid (refill audit, 12 mo): (1) asthma: I = 57, C = 32, Δ = 25, P = .04; (2) COPD: I = 50, C = 58, Δ = 8, P = NS</td>
<td>(1) Medium, 0.51 (0.04 to 0.98); (2) none, 0.16 (−0.70 to 0.38)</td>
<td>Change in FEV, (mean ± SD, 12 mo): (1) asthma: I = 112 ± 38 ml, C = 83 ± 38 ml, Δ = 195 ml, P = .05; (2) COPD: I = 97 ml, C = 50 ml, Δ = 47 ml, P = NS†</td>
<td>(1) Medium, 0.52 (0.04 to 0.99); (2) NA‡</td>
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<td>Hill et al.23,2001</td>
<td>Rheumatoid arthritis, I = 51, C = 49</td>
<td>I: Individual education (7-30-min sessions). C: Usual care (drug information leaflet).</td>
<td>Adherence ≥85% (plasma levels of pharmacological marker, 24 wk): I = 85, C = 55, Δ = 30, P = .01</td>
<td>Medium, 0.68 (0.22 to 1.13)</td>
<td>(1) Articular index (mean, range): I = 15.9 (0-41), C = 13.7 (0-58), Δ = 2.2, P = .33; (2) morning stiffness (in minutes): I = 49 (0-308), C = 50 (0-190), Δ = 1, P = .41; (3) pain score: I = 2.38 (1-3.28), C = 2.55 (1.14-4.50), Δ = −0.17, P = .44†</td>
<td>(1) None, −0.19 (−0.64 to 0.27)§; (2) none, 0.02 (−0.44 to 0.47)§; (3) none, 0.25 (−0.20 to 0.71)§</td>
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<td>Laporte et al.24,2003</td>
<td>Thromboembolic disease, I = 43, C = 43</td>
<td>I: Intensive education (written material, daily nurse and physician visits while in hospital, daily tests about education, emphasis on adherence). C: Standard education (basic information, no emphasis on adherence).</td>
<td>(1) % Correct bottle openings (MEMS caps, mean ± SD, 3 mo): I = 84.5 ± 17.7, C = 80.7 ± 19.4, Δ = 3.8, P = .36; (2) % of prescribed pills taken (pill count, 3 mo): I = 99.7 ± 15.1, C = 100.6 ± 18.2, Δ = 0.9, P = .82</td>
<td>(1) None, 0.23 (−0.34 to 0.54); (2) NA‡</td>
<td>(1) % of INRs in target range (mean ± SD, 3 mo): I = 51.3 ± 17.5, C = 55.9 ± 16.1, Δ = 4.6, P = .23; (2) % of time in target INR range (mean ± SD, 3 mo): I = 81.6 ± 17.6, C = 65.8 ± 17.6, Δ = 4.2, P = .28</td>
<td>(1) None, −0.09 (−0.53 to 0.34); (2) none, −0.08 (−0.52 to 0.35)</td>
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<tr>
<td>Levy et al.23,2000</td>
<td>Asthma, I = 103, C = 108</td>
<td>I: Individual education by nurse (1-h session, then two 30-min sessions at 6-week intervals), self-management plan based on PEF or symptom monitoring. C: Usual care.</td>
<td>Increased use of inhalers for asthma attacks (self-report, 8 mo): (1) inhaled steroids for mild attacks: I = 47, C = 23, Δ = 24, P = .11; (2) rescue medications for mild attacks: I = 89, C = 82, Δ = 7, P = .87; (3) inhaled steroids for severe attacks: I = 51, C = 21, Δ = 24, P &lt; .001; (4) rescue medications for severe attacks: I = 89, C = 76, Δ = 13, P &lt; .05</td>
<td>(1) None, 0.51 (−0.10 to 1.12); (2) none, 0.20 (−0.41 to 0.81); (3) medium, 0.64 (0.30 to 0.98); (4) small, 0.35 (0.01 to 0.69)</td>
<td>(1) PEF (6 mo): I = 20.1 L/min, C = 15.5 L/min, Δ = 4.6, P = .07; (2) severe attacks (6-week period): I = 34, C = 42, Δ = −8, P = NS; (3) symptom scores (mean ± SD, 6 mo): I = 45.5 ± 22.0, C = 38.1 ± 22.0, Δ = 7.6, P&lt;.001; (4) routine physician visits (median, range): I = 1 (1-6), C = 1 (1-3), Δ = 0, P = NS; (5) emergency department visits (median, range): I = 0 (1-7), C = 0 (1-7), Δ = 0, P = NS</td>
<td>(1) None, 0.15 (−0.14 to 0.44); (2) none, −0.17 (−0.46 to 0.15); (3) small, 0.34 (0.06 to 0.62); (4) none, 0.00 (−0.34 to 0.34)§; (5) none, 0.00 (−0.34 to 0.34)§</td>
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<tr>
<td>Moncur and Wrench.20,2001</td>
<td>Asthma, I = 40, C = 40</td>
<td>I: Individual inpatient education by nurse (two 30-min sessions), booklet, self-management plan based on PEF. C: Usual care.</td>
<td>Self-reported adherence (8 mo): similar in I and C</td>
<td>NA‡</td>
<td>Urgent visits, call-outs, or readmission (NI): I = 25, C = 25, Δ = 0, P = NS</td>
<td>None, −0.29 (−0.77 to 0.20)</td>
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(continued)
significant improvement in blood pressure, whereas Girvin et al.\(^\text{36}\) actually found a trend toward increased blood pressure in the once-daily therapy group.

The 4 trials that involved assessment and feedback asked patients to monitor and report their medication use and/or blood pressure.35\,37\,39 The 3 studies that then provided patients with tailored feedback, reinforcement, or rewards demonstrated a significant improvement in adherence (ESs small to large; range, 0.27–0.81).35\,37\,39 The fourth study, which simply made home blood pressure values available to the patient and physician, did not improve adherence.38 Only 1 study in this group produced a clear improvement in clinical outcomes (Marquez Contreras et al.\(^\text{39}\)), ES = 0.93 for total cholesterol and 0.78 for low-density lipoprotein cholesterol). Friedman and colleagues\(^\text{35}\) reported a decrease in the diastolic blood pressure only after controlling for baseline blood pressure in adjusted analyses (small ES of 0.29); they found no significant change for systolic blood pressure.

**COMBINED INTERVENTIONS**

Most (13 of 15) combined interventions included informational and behavioral components,42\,43\,47\,48 and 2 joined social support strategies with either informational or behavioral elements (Table 3).\(^\text{50,56}\) Sample size again varied widely, from 37 to 1113. Of the 13 studies with informational

### Table 1. Informational Interventions (cont)

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<tr>
<th>Source</th>
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<tr>
<td>Peterson et al.(^\text{33}) 2004</td>
<td>Dyslipidemia, I = 45, C = 49</td>
<td>I: Home visits by pharmacist (monthly for 6 mo); included counseling on medication and lifestyle changes, assessment of side effects, point-of-care cholesterol testing. C: Usual care.</td>
<td>Self-reported adherence (6 mo): no change</td>
<td>NA‡</td>
<td>Cholesterol levels (mean ± SD): I = 4.4 ± 0.6 mmol/L, C = 4.6 ± 0.8 mmol/L, ( \Delta = 0.2 ) mmol/L, ( P = 0.24 )</td>
<td>None, 0.29 (−0.72 to 0.15)</td>
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<tr>
<td>Pradier et al.(^\text{36}) 2003</td>
<td>HIV, I = 124, C = 122</td>
<td>I: Individually delivered session focused on cognitive, emotional, social and behavioral determinants affecting adherence (34–60-min sessions). C: Usual care.</td>
<td>100% Adherence (self-report, 6 mo): I = 75, C = 61, ( \Delta = 14, P = 0.04 )</td>
<td>Large, 1.13 (0.86 to 1.41)</td>
<td>Change in HIV RNA from baseline (mean ± SD, 6 mo): I = −0.22 ± 0.86 log copies/mL, C = −0.12 ± 0.90 log copies/mL, ( \Delta = −0.34 ) log copies/mL, ( P = 0.002 )</td>
<td>Small, −0.39 (−0.64 to −0.14)</td>
</tr>
<tr>
<td>Rawlings et al.(^\text{37}) 2003</td>
<td>HIV, I = 96, C = 99</td>
<td>I: Small group sessions led by health care professional, focusing on patient empowerment; HIV treatment, and medication management (weekly for 4 wk); used flip charts, videotapes, patient logbooks, and patient workbooks, plus routine adherence counseling. C: Routine adherence counseling.</td>
<td>% of Prescribed doses taken (MEMS caps, 6 mo): I = 70, C = 74 ( \Delta = −4, P = \text{NS} )</td>
<td>None, −0.09 (−0.37 to 0.19)</td>
<td>% With HIV RNA &lt; 40 copies/mL (24 wk): I = 60, C = 55, ( \Delta = 5, P = 0.53 )</td>
<td>None, 0.10 (−0.25 to 0.46)</td>
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<tr>
<td>Schaffer and Tian(^\text{38}) 2004</td>
<td>Asthma, I = 10, I = 12, I = 11, C = 13</td>
<td>I: Audiointake alone (I), booklet alone (I), or audiointake plus booklet (I). C: Usual care (standard provider education).</td>
<td>% of Doses filled (refill audit, 6 mo): I = 48, I = 77, I = 77, C = 49; (1) none, ( \Delta = 8, P = 0.17 ); (2) none, ( \Delta = 37, P = 0.02 ); (3) none, ( \Delta = 34, P = 0.04 )</td>
<td>(1) none, 0.16 (−0.66 to 0.99); (2) none, 0.77 (−0.01 to 1.56); (3) none, 0.77 (−0.03 to 1.57)</td>
<td>Asthma control questionnaire (6 mo): I = 1.47, I = 1.30, C = 1.25; (1) none, ( \Delta = 0.22, P = 0.50 ); (2) none, ( \Delta = 0.95, P = 0.40 ); (3) none, ( \Delta = 0.05, P = 0.90 )</td>
<td>(1) none, 0.30 (−0.53 to 1.13); (2) none, 0.36 (−0.43 to 1.15); (3) none, 0.11 (−0.69 to 0.91)</td>
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<td>van Es et al.(^\text{39}) 2001</td>
<td>Asthma, N = 112</td>
<td>I: Discussion of self-management plan with pediatrician, individual education by nurse (4-35 min sessions), group education (30-90 min sessions). C: Usual care (pediatrician every 4 mo).</td>
<td>Self-reported adherence (10-point scale, mean ± SD, 12 mo): I = 7.8 ± 1.6, C = 7.3 ± 1.8, ( \Delta = 0.5, P = 0.14 )</td>
<td>None, 0.30 (−0.13 to 0.73)</td>
<td>FEV\textsubscript{1}/FVC (mean ± SD, 12 mo): I = 96.2 ± 17.0, C = 96.2 ± 13.4, ( \Delta = 0.07, P = 0.83 ); (2) none, 0.38 (−0.82 to 0.06)</td>
<td>(1) none, −0.05 (−0.47 to 0.37); (2) none, 0.38 (−0.82 to 0.06)</td>
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Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; DMPA, depot-medroxyprogesterone acetate; ES, effect size; FEV\textsubscript{1}, forced expiratory volume in 1 second; FVC, forced vital capacity; HIV, human immunodeficiency virus; I, intervention; INR, international normalized ratio; MEMS, medication event monitoring system; NA, not available; NS, not significant; PEF, peak expiratory flow; PRECEDE, Predisposing, Reinforcing, Enabling, Causes in, Educational Diagnosis and Evaluation; \( \Delta \), difference between intervention and control groups.

* Exact values not provided in article. Results are estimated from a figure.
† Results obtained or confirmed by personal communication with authors.
‡ Could not be calculated with available data.
§ The ES was calculated by converting range into standard deviation.
¶ The ES was calculated by using median instead of mean. 
# Lower score indicates better asthma control.
<table>
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<tr>
<th>Source</th>
<th>Hypertension</th>
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<th>ES (95% CI) for Clinical Outcome</th>
</tr>
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</table>
| Baird et al.  
1984 | Hypertension | I = 196, C = 193 | Metropolit once a day; C: Metropolit twice a day. | % of Prescribed pills taken (pill count, 10 wk): I = 66.0, C = 54.1, p = 0.19, P = NS; (2) = 0.80% of prescribed pills taken (pill count: I = 84, C = 73, p = 0.19, P = NS | NA* | DBP 2 mo: I = 85.3 mm Hg, C = 88.8 mm Hg, Δ = 3.5 mm Hg, P = NS | NA* |
| Becker et al.  
1986 | Hypertension | I = 86, C = 85 | Special reminder (blister) packaging of anti-hypertensives; T: Traditional pill bottles. | (1) = 100% Adherence (self-report): I = 56.0, C = 54.1, Δ = 1.9, P = NS; (2) = 80% of prescribed pills taken (pill count: I = 84, C = 73, Δ = 0.07, P = NS | NA* | DBP 3 mo: I = 85.3 mm Hg, C = 88.8 mm Hg, Δ = 3.5 mm Hg, P = NS | NA* |
| Brown et al.  
1997 | Dyslipidemia | N = 31 (crossover study) | Controlled release niacin given a day; C: Regular niacin 4 times a day. | % of prescribed pills taken (pill count, 8 mo): I = 96, C = 96, Δ = 0.1, P = 0.1 | Large, 0.89 (0.38 to 1.41) | Achieved LDL-C ≤ 100 (8 mo): I = 83, C = 52, Δ = 31, P = 0.21 | Medium, 0.66 (0.15 to 1.18) |
| Friedman et al.  
1996 | Hypertension | N = 299 (results available for I = 133, C = 134) | Telephone-linked computer system to assess adherence, side effects, knowledge, and BP (weekly for 6 mo); feedback given to patient and physician. | Change in adherence (pill count, 6 mo): I = 17.7, C = 11.7, Δ = 6, P = 0.3 | Small, 0.27 (0.03 to 0.51) | (1) = Decrease in SBP (6 mo): I = 11.5 mm Hg, C = 6.8 mm Hg, Δ = 4.7 mm Hg, P = 0.005 | (1) = None, 0.16 (−0.08 to 0.40); (2) = small, 0.29 (0.05 to 0.53) |
| Girvin et al.  
1999 | Hypertension | N = 27 (crossover study) | Enalapril, 20 mg once daily; C: Enalapril, 10 mg twice daily. | % of prescribed doses taken (mean with 95% CI, 12th month): I = 65.8, C = 43.2, Δ = 22.6, P = 0.02 | Medium, 0.78 (0.12 to 1.44) | DBP (mean ± SD, 12 mo): I = 93.1 ± 13.3 mm Hg, Δ = −3.3 mm Hg, P = .005 | None, −0.60 (−1.25 to 0.05) |
| Haynes et al.  
1976 | Hypertension | I = 20, C = 19 | Self-monitoring of pills and blood pressure, tailored medication schedule, home visits by research assistant, rewards. | % of prescribed doses taken (pill count, 12th month): I = 65.8, C = 43.2, Δ = 22.6, P = 0.02 | NA* | DBP (mean ± SD, 12 mo): I = 93.1 ± 13.3 mm Hg, Δ = −3.3 mm Hg, P = .005 | NA* |
| Johnson et al.  
1978 | Hypertension | I = 35, C = 35 | Hypertension, I = 86, C = 85 | % of prescribed doses taken (pill count and interview, 6 mo): I = 76.3, C = 76.3, Δ = 0.0, P = NS | NA* | NA* | NA* |
| Marquez Contreras et al.  
2004 | Dyslipidemia | I = 63, C = 63 | 3 Telephone calls (at 7–10 d, 2 mo, and 4 mo) to assess adherence, provide feedback, and give a tailored recommendation. | % of prescribed doses taken (pill count, mean ± SD, 6 mo): I = 93.0 ± 8.2, C = 84.4 ± 12.8, Δ = 8.6, P = 0.001 | Large, 0.81 (0.43 to 1.19) | (1) = Decrease in total cholesterol (mean ± SD, 6 mo): I = 64.7 ± 35 mg/dL, C = 33.1 ± 37 mg/dL, Δ = 31.6 mg/dL, P = 0.005; (2) = decrease in LDL-C (mean ± SD, 6 mo): I = 63.2 ± 27 mg/dL, C = 53.8 ± 42 mg/dL, Δ = 27.6 mg/dL, P = 0.001 | Large, 0.89 (0.50 to 1.27); (2) medium, 0.78 (0.41 to 1.16) |
| Walley et al.  
2001 | Tuberculosis | I = 170, C = 166 | Direct observation of therapy by health workers (I), or direct observation of treatment by family members (I). | Compliant with collecting medications from health center (8 mo): I = 73, C = 68, Δ = 5, P = NS | (1) = None, 0.13 (−0.09 to 0.36); (2) = none, 0.02 (−0.20 to 0.24 | (1) = Cure rate (8 months): I = 64, C = 55, Δ = 9, P = 0.04; (2) = none, 0.02 (−0.18 to 0.27); (3) = none, −0.14 (−0.62 to 0.33); (4) = none, −0.14 (−0.62 to 0.34); | (1) = none, 0.00 (−0.45 to 0.49); (2) = none, −0.14 (−0.62 to 0.33); (3) = none, −0.14 (−0.62 to 0.34); |
| Weber et al.  
2004 | HIV, I = 32, C = 29 | Cognitive behavior therapy (5–25 sessions during 1 yr). | % of prescribed doses taken (MMS, 10–12 months): I = 92.8, C = 88.9, Δ = 3.9, P = 0.15 | None, 0.14 (−0.41 to 0.68) | (1) = Undetectable viral load: I = 72.4, C = 79.2, Δ = −6.8, P = NS; (2) = CD4 count (median with range): I = 407.5 (203–955), C = 495 (95–1976), Δ = −82.5, P = NS | None, 0.16 (−0.70 to 0.39); (2) = none, −0.26 (−0.80 to 0.28) |

Abbreviations: BP, blood pressure; C, control; CI, confidence interval; DBP, diastolic blood pressure; ES, effect size; HIV, human immunodeficiency virus; I, intervention; LDL-C, low-density lipoprotein cholesterol; MEMS, medication event monitoring system; NA, not available; NS, not significant; SBP, systolic blood pressure; Δ, difference between intervention and control groups.

*Could not be calculated with available data.

†Adjusted for age, sex, baseline BP and baseline adherence; unadjusted analyses showed no significant difference.

‡Night-time SBP and DBP also showed a trend toward higher values in the intervention group.

§Nonadherence was defined as failing to collect medications for 2 consecutive months.

‖Adherence also compared by a 10-point visual analog scale, I = 9.93, C = 9.80, Δ = 0.13, P = .012.

¶The ES was calculated by using median instead of mean and by converting range to standard deviation.
and behavioral elements, 5 demonstrated improvement in all adherence measures, 42,47,48,50,51 and 3 others reported mixed or nearly significant results.53,45 The significant effects ranged in size from small to large (absolute ES values of 0.43-1.20). No studies in this group were able to demonstrate a significant change in all measured clinical parameters, although several trials noted a significant improvement in at least 1 clinical outcome.42,48,51,55 Or a strong trend.53 The ESs ranged widely across studies (very small to large ES [0.17-1.58]). No consistent relationships were observed between intervention characteristics or disease state and the success of the interventions. For example, 3 trials implemented relatively similar interventions among patients with asthma, but their reported effects varied substantially.45,46,47 Regarding the 2 studies with strong social support elements, both successfully improved adherence (unable to calculate ES), but neither led to better clinical outcomes.56,57

COMMENT

In this systematic review of randomized controlled trials designed to enhance medication adherence in chronic medical conditions, 16 of 37 trials reported a consistent improvement in adherence.* Four other studies noted a significant change in adherence among a particular patient subgroup, with some but not all of the adherence measures used, or in a certain arm of a study testing multiple interventions.19,20,25,30,43 Nine of the 20 trials that had some impact on adherence were able to demonstrate an improvement in some.10,20,23,35,42,48,51 or all18,28,34,39 of the measured clinical outcomes. Of the 17 studies that did not show an improvement in adherence, 2 improved clinical outcomes; the apparent lack of effect on adherence in these studies was probably due to insensitive adherence measures or a ceiling effect.22,33 Previous reviews have found few if any consistent relationships between the characteristics and effectiveness of interventions to improve adherence.7 In the present study, categorization of the trials by intervention type (informational, behavioral, or combined informational, behavioral, and/or social support) and calculation of ESs permit a few general observations. Behavioral interventions that reduced the dosing demands of individual therapies consistently improved adherence with a large ES (0.89-1.20). Apart from this, other successful interventions usually contained multiple elements delivered over time. For example, 6 informational interventions that provided educational counseling over a few sessions and addressed self-care issues improved adherence with small to large ESs (0.35-1.13). Successful behavioral interventions based in monitoring and feedback and the most successful combined interventions also included various elements, such as self-management plans, reinforcement, and occasionally rewards.

Despite the ability of these interventions to improve adherence, however, a positive effect on clinical outcomes was demonstrated infrequently, and ESs pertaining to clinical outcomes were highly variable (very small to large ES [0.17-3.41]). Moreover, results for clinical outcomes were not consistently related to the magnitude of adherence results or the characteristics of the intervention. Unfortunately, many of the studies were relatively small and not sufficiently powered to detect differences in clinical outcomes. Thus, the results of many of the studies are indeterminate for clinical outcome, rather than clearly negative.

The adherence literature and present study had several additional limitations. First, because we included only published trials, the reported findings may overestimate the true effect of such interventions due to publication bias. Second, our inclusion criteria were somewhat stringent. Many studies with shorter follow-up or no measurement of clinical outcomes were excluded, and they are listed elsewhere.12 Third, our ability to categorize the trials into distinct modes of intervention was limited by the frequently complex nature of the interventions, requiring us to make judgments about the predominant components. Fourth, although we calculated ES and can make general comments about the magnitude of adherence and clinical outcome differences, the included studies were too heterogeneous to warrant pooling in a formal meta-analysis. Fifth, the literature review was completed in September 2004 and trials published since then may differ in their results, although they would be unlikely to substantially change the conclusions drawn from the 37 trials included in this review.

Because most of the available literature does not separate out the effects of the individual components of multifaceted interventions, it is not possible to draw definitive conclusions about which features of combined interventions are most beneficial. Additional research is needed to clarify which features are most responsible for changes in adherence and clinical outcomes, with the caveat that individual components may not prove powerful enough to show important effects. Future studies should also examine the effect of varying the intensity of interventions to determine dose-response relationships. Such findings would have important implications for health systems considering the implementation of patient adherence programs on a large scale. Investigations should be conducted with clinically meaningful outcomes as the primary end points and be sufficiently powered to detect a difference in these measures. Most important, future research should seek to understand the determinants of adherence behavior and to develop and test innovative ways to help people adhere to prescribed medication regimens, rather than persisting with existing approaches.

In summary, we found that several types of interventions are effective in improving medication adherence, but few were able to demonstrate an impact on clinical

Table 3. Combined Interventions

<table>
<thead>
<tr>
<th>Source</th>
<th>Population and Sample Sizes</th>
<th>Intervention/Control</th>
<th>Adherence Measures and Results, %</th>
<th>ES (95% CI) for Adherence</th>
<th>Clinical Outcome Measures and Results, %</th>
<th>ES (95% CI) for Clinical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bailey et al,42 1990</td>
<td>Asthma, I = 132, C = 135</td>
<td>I: Educational pamphlets, workbook, tailored self-management plan, individual counseling session, support group, telephone follow-up, reinforcement. C: Usual care (educational physician encouragement).</td>
<td>(1) Self-reported adherence to inhaler (≥5 of 6 items, 12 mo): I = 86.1, C = 55.9, Δ = 30.2, P &lt; .001; (2) self-reported adherence to medications (≥5 of 6 items, 12 mo): I = 96.0, C = 82.7, Δ = 13.3, P &lt; .005; (3) adherence rated excellent by staff (12 mo): I = 78.3, C = 51.6, Δ = 27.3, P &lt; .001</td>
<td>(1) Medium, 0.69 (0.43 to 0.95); (2) small, 0.46 (0.19 to 0.72); (3) medium, 0.58 (0.32 to 0.84)</td>
<td>Self-report (12 mo): I = 11.4, C = 27.3, Δ = −15.6, P &lt; .002; (2) bothered by asthma in past 7 d: I = 64.6, C = 75.0, Δ = −10.4, P &lt; .11; (3) ≥5 episodes in past 3 mo: I = 17.5, C = 47.4, Δ = −29.9, P &lt; .001; (4) asthma interfered with life in past 3 mo: I = 52.0, C = 56.1, Δ = −6.2, P &lt; .13</td>
<td>(1) Small, −0.40 (−0.67 to −0.14); (2) none, −0.23 (−0.49 to 0.04); (3) medium, −0.86 (−0.92 to −0.39); (4) none, −0.12 (−0.39 to 0.14)</td>
</tr>
<tr>
<td>Beren et al,44 2004</td>
<td>HIV, I = 20, C = 17</td>
<td>I: Structured nurse home visits during 3 mo to educate, identify and resolve barriers, and provide incentives; included notebooks and pill-swallowing training. C: Usual care (medication pills, reminders, emotional support, nurse telephone call as needed, 1 home visit if adherence poor).</td>
<td>(1) Refill score (4 points): I = 2.7, C = 1.7, Δ = 1.0, P &lt; .002; (2) self-reported adherence (change from baseline, mean ± SEM, 3 mo): I = 2.7 ± 0.88, C = 0.2 ± 0.96, Δ = 2.5, P = .07</td>
<td></td>
<td>Undetectable viral load (6-11 mo): I = 45.5, C = 23.5, Δ = 21.9, P &lt; NS</td>
<td>None, 0.46 (−0.29 to 1.11)</td>
</tr>
<tr>
<td>Brus et al,46 1998</td>
<td>Rheumatoid arthritis, I = 29, C = 31</td>
<td>I: Group patient educational meetings (4 2-h meetings during the first months, reinforcement meetings at 4 and 8 mo); partners invited; included counseling on adherence, energy conservation, joint protection, physical activity education and training, behavioral contract, and feedback. C: Brochure on rheumatoid arthritis.</td>
<td>% of Prescribed doses taken (pill count, mean ± SD, 6-12 mo): I = 89 ± 16, C = 84 ± 21, Δ = 5 ± 6, P &lt; NS</td>
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<tr>
<td>Cote et al,45 1997</td>
<td>Asthma, N = 188 (I1 = 50, I2 = 45, C = 54 completed the study)</td>
<td>I: Asthma education program (1 h) with book and written action plan based on peak flow monitoring with reminding and reinforcing at each visit (I1) or symptom monitoring (I2). C: Usual care (physician prescription, inhaler technique, and possibly oral symptom triggers, inhaler technique, and possibly oral action plan).</td>
<td>≥60% of Prescribed doses taken (weight of used canisters, 12 mo): P &lt; .06</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coull et al,46 2004</td>
<td>Ischemic heart disease, I = 165, C = 154</td>
<td>I: Monthly informational or supportive group meetings (2 h) led by lay health mentors. C: Usual care.</td>
<td>Self-reported adherence (12 mo): P &lt; .01</td>
<td></td>
<td>Total events (mean, 12 mo): I = 0.38, C = 0.39, Δ = −0.01, P &lt; NS</td>
<td>NA*</td>
</tr>
<tr>
<td>Farber and Olivera,46 2004</td>
<td>Asthma, I = 28, C = 28</td>
<td>I: Basic asthma education, written self-management plan, prescriptions, holding chamber, and 3 follow-up calls to reinforce plan at 1-2 wk, 3-4 wk, and 3 mo. C: Usual care.</td>
<td>Dispensing events of controlling medications (eq. corticosteroids) (mean, 6 mo): I = 21.1, C = 6.33, Δ = 14.7, P &lt; .004</td>
<td>Large, 0.87 (0.29 to 1.44)</td>
<td>Urgent visits for asthma exacerbation: I = 43, C = 36, Δ = 7, P &lt; .56</td>
<td>None, 0.14 (−0.41 to 0.70)</td>
</tr>
<tr>
<td>Knobel et al,46 1999</td>
<td>HIV, I = 65, C = 121</td>
<td>I: Individual counseling, detailed information about medications, tailored medication schedule, telephone support, monthly clinic visits. C: Usual care.</td>
<td>≥90% of Prescribed doses taken (pill count, 24 wk): I = 76.7, C = 52.7, Δ = 24, P &lt; .002</td>
<td>Medium, 0.51 (0.19 to 0.82)</td>
<td>(1) Undetectable viral load (24 wk): I = 65.0, C = 54.4, Δ = 10.6, P &lt; .18; (2) reduction in viral load (mean ± SD, 24 wk): I = 1.98 ± 0.78 log10/mL, C = 1.02 ± 0.5 log10/mL, Δ = 0.96 log10/mL, P &lt; .04; (3) increase in CD4 cell count (mean ± SD, 24 wk): I = 96.3 ± 56, C = 55.1 ± 33, Δ = 41.2, P &lt; .001</td>
<td>(1) None, 0.22 (−0.10 to 0.53); (2) large, 1.58 (1.22 to 1.93); (3) large, 0.98 (0.84 to 1.13)</td>
</tr>
</tbody>
</table>

(continued)
### Table 3. Combined Interventions (cont)

<table>
<thead>
<tr>
<th>Source</th>
<th>Population and Sample Size</th>
<th>Intervention/Control</th>
<th>Adherence Measures and Results, %</th>
<th>ES (95% CI) for Adherence</th>
<th>Clinical Outcome Measures and Results, %</th>
<th>ES (95% CI) for Clinical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piette et al, 2000</td>
<td>Diabetes, I = 137, C = 143</td>
<td>I: Automated telephone assessment and tailored education with reminders, reinforcement, and nurse follow-up; C: Usual care.</td>
<td>Self-reported adherence (median: 6 mo): i = 0.46, C = 0.46, Δ = 0, P = NS</td>
<td>None, 0.08 to 0.18</td>
<td>None, 0.66 to 0.18</td>
<td>None, 0.26 to 0.08</td>
</tr>
<tr>
<td>Sackett et al, 1975</td>
<td>Hypertension, I = 37, C = 25</td>
<td>I: &gt; 2 x factorial design; care at worksite by occupational health physicians (i), programmed education and adherence reminders (i), or both interventions (i). C: Usual care.</td>
<td>Self-reported adherence (12 mo): i = 0.8, C = 0.8, Δ = 0, P = NS</td>
<td>None, 0.08 to 0.33</td>
<td>None, 0.08 to 0.33</td>
<td>None, 0.19 to 0.40</td>
</tr>
<tr>
<td>Tuldra et al, 2000</td>
<td>HIV, I = 55, C = 61</td>
<td>I: Psychosocial intervention to improve knowledge and self-efficacy, tailored medication schedule, telephone number provided, oral reinforcement at clinic visits. C: Usual care.</td>
<td>Self-reported adherence (48 wk): i = 0.58, C = 0.41, Δ = 0.17, P = 0.06</td>
<td>None, 0.05 to 0.73</td>
<td>None, 0.05 to 0.73</td>
<td>None, 0.13 to 0.65</td>
</tr>
<tr>
<td>Volume et al, 2001</td>
<td>Elderly with 3 medications, I = 159, C = 204</td>
<td>I: Comprehensive pharmaceutical care services including 30- to 45-min individual assessment by pharmacist and frequent follow-up communication, with standard documentation of contacts. C: Usual care (pediatric endocrinology contact triggered by prescriptions).</td>
<td>Self-reported adherence (4-item scale, mean ± SD, 12-13 mo): i = 0.56 ± 0.75, C = 0.47 ± 0.69, Δ = 0.09, P = NS</td>
<td>None, 0.13</td>
<td>None, 0.08 to 0.33</td>
<td>None, 0.02 to 0.40; 0.03 to 0.40</td>
</tr>
<tr>
<td>Weinberger et al, 2002</td>
<td>Asthma and COPD, I = 447, C = 363, C = 303</td>
<td>I: Pharmaceutical care program including review of monthly PEF data, adherence, and health care utilization; patient education materials; and other resources to facilitate pharmacist intervention. C: Usual care (patient contact triggered by prescriptions).</td>
<td>Self-reported adherence (4-item scale, mean ± SD, 12 mo): i = 0.8 ± 0.1, C = 0.8 ± 0.1, P = 0.57</td>
<td>None, 0.13</td>
<td>None, 0.08 to 0.33</td>
<td>None, 0.02 to 0.40; 0.03 to 0.40</td>
</tr>
<tr>
<td>Wysocki et al, 2001</td>
<td>Diabetes, I = 38, C = 41</td>
<td>I: Behavior-family systems therapy (10 sessions), monetary incentive; C: education and support (10 group educational and social support meetings), monetary incentive. C: Usual care (pediatric endocrinology follow-up, self-management training).</td>
<td>Self-care inventory (change characteristic over 6 mo): (1) NA*, (2) I-C: Δ = 0.2</td>
<td>None, 0.01 to 0.02</td>
<td>None, 0.13 to 0.39</td>
<td>None, 0.11 to 0.39</td>
</tr>
</tbody>
</table>

Abbreviations: C, control; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; ES, effect size; HbA1c, hemoglobin A1c; HIV, human immunodeficiency virus; HRQOL, health-related quality of life; I, intervention; NA, not available; NS, not significant; PEF, peak expiratory flow; SF-36, 36-item Short-Form Health Survey; Δ, difference between intervention and control groups.

*Could not be calculated with available data.
†P value recalculated from results in article.
‡Lower score indicates better adherence.
§Intervention group had more recent visits than control groups.
∥Results obtained or confirmed by personal communication with authors.
¶Higher score indicates better adherence.
outcomes. Based on this review of the literature, the most effective interventions appear to be those that simplify dosing demands. Interventions that involve monitoring and feedback, as well as informational interventions delivered over multiple sessions, are probably also effective.

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Correspondence: Sunil Kripalani, MD, MSc, Division of General Medicine, Department of Internal Medicine, Emory University School of Medicine, 49 Jesse Hill Jr Dr SE, Atlanta, GA 30303 (skripal@emory.edu).

Author Contributions: Dr Kripalani had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Kripalani and Haynes. Acquisition of data: Kripalani, Yao, and Haynes. Analysis and interpretation of data: Kripalani, Yao, and Haynes. Drafting of the manuscript: Kripalani, Yao, and Haynes. Critical revision of the manuscript for important intellectual content: Kripalani and Yao. Statistical analysis: Kripalani and Yao. Obtained funding: Haynes. Administrative, technical, and material support: Yao and Haynes. Study supervision: Kripalani and Haynes.

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