

# Interventions to Enhance Patient Adherence to Medication Prescriptions

## Scientific Review

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**A**DHERENCE MAY BE DEFINED AS the extent to which a patient's behavior (in terms of taking medication, following a diet, modifying habits, or attending clinics) coincides with medical or health advice.<sup>1,2</sup> If a patient is prescribed an antibiotic for an infection to be taken as 1 tablet 4 times a day for a week but takes only 2 tablets a day for 5 days, the adherence would be 36% (10/28). The term adherence is intended to be non-judgmental, a statement of fact rather than of blame of the prescriber, patient, or treatment. Compliance and concordance are synonyms for adherence.

This simple definition of adherence belies the difficulties that many medical regimens present for patients. For example, the regimen described for type 2 diabetes mellitus in a previous article<sup>3</sup> includes a special diet, increased exercise, smoking cessation, oral hypoglycemic drugs, and risk factor management, usually involving additional drugs. Such regimens fulfill theoretical, physiological, and empirical considerations about optimal care, while ignoring practical patient-centered concerns, such as the nature, nurture, culture, and stereotyping of the patient, and the inconvenience, cost, and

**Context** Low adherence with prescribed treatments is ubiquitous and undermines treatment benefits.

**Objective** To systematically review published randomized controlled trials (RCTs) of interventions to assist patients' adherence to prescribed medications.

**Data Sources** A search of MEDLINE, CINAHL, PSYCHLIT, SOCIOFILE, IPA, EMBASE, The Cochrane Library databases, and bibliographies was performed for records from 1967 through August 2001 to identify relevant articles of all RCTs of interventions intended to improve adherence to self-administered medications.

**Study Selection and Data Extraction** Studies were included if they reported an unconfounded RCT of an intervention to improve adherence with prescribed medications for a medical or psychiatric disorder; both adherence and treatment outcome were measured; follow-up of at least 80% of each study group was reported; and the duration of follow-up for studies with positive initial findings was at least 6 months. Information on study design features, interventions, controls, and findings (adherence rates and patient outcomes) were extracted for each article.

**Data Synthesis** Studies were too disparate to warrant meta-analysis. Forty-nine percent of the interventions tested (19 of 39 in 33 studies) were associated with statistically significant increases in medication adherence and only 17 reported statistically significant improvements in treatment outcomes. Almost all the interventions that were effective for long-term care were complex, including combinations of more convenient care, information, counseling, reminders, self-monitoring, reinforcement, family therapy, and other forms of additional supervision or attention. Even the most effective interventions had modest effects.

**Conclusions** Current methods of improving medication adherence for chronic health problems are mostly complex, labor-intensive, and not predictably effective. The full benefits of medications cannot be realized at currently achievable levels of adherence; therefore, more studies of innovative approaches to assist patients to follow prescriptions for medications are needed.

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adverse effects of the treatment. Indeed, low adherence with prescribed treatments is very common. Typical ad-

herence rates for prescribed medications are about 50% with a range of 0% to more than 100%.<sup>4</sup>

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See also p 2880.

At a theoretical level, the nature and determinants of noncompliant behavior are complex and not well understood, although there are interesting models.<sup>5</sup> The following generalizations stem from numerous studies of the determinants of adherence.<sup>5-7</sup> Compliance has little relation to sociodemographic factors such as age, sex, race, intelligence, and education. Also, although low adherence is a problem with self-administered treatments for all disorders, patients with psychiatric problems are less likely to comply and those with physical disabilities caused by the disease are more likely to comply. In addition, patients tend to miss appointments and drop out of care when there are long waiting times at clinics or long time lapses between appointments. Finally, adherence decreases as the complexity, cost, and duration of the regimen increase.

To the extent that treatment response is related to the dose and schedule of a therapy, nonadherence reduces treatment benefits<sup>8</sup> and can bias assessment of the effectiveness of treatments.<sup>5,9</sup> In addition to its potential for undermining the effectiveness of any treatment, nonadherence is associated with poorer prognosis.<sup>10</sup> With increasing numbers of effective self-administered treatments, the need is apparent for better understanding and management of nonadherence. We review evidence from randomized controlled trials (RCTs) of interventions to assist patients to follow prescribed medications for medical or mental disorders but not for addictions.

## METHODS

Literature searches were completed from 1967 to August 2001 without language restrictions through MEDLINE, CINAHL, PSYCHLIT, SOCIOFILE, IPA, EMBASE, and The Cochrane Library databases to identify all articles of RCTs involving interventions intended to improve adherence to self-administered medications. At least 2 of the 3 reviewers independently screened all citations, index terms, abstracts if available, and any article considered po-

tentially relevant by either reviewer was retrieved. Bibliographies of other reviews and original trial publications were also screened for potentially relevant studies. Authors of included trials were contacted to suggest other published or unpublished trials that had been missed.

Studies were selected for inclusion from potentially relevant full-text articles if they reported an unconfounded RCT (ie, having no baseline variables or interventions that are extraneous to the study question but potentially related to the outcome and differentially applied to the intervention and control groups) of an intervention to improve adherence with prescribed medications for a medical or psychiatric disorder, measuring both medication adherence and treatment outcome, with at least 80% follow-up of each group studied and, for long-term treatments, at least 6 months follow-up for studies with positive initial findings. Negative trials with shorter follow-up periods were included on the grounds that initial failure was unlikely to be followed by success.<sup>4</sup> The criterion for assessment of both adherence and outcome was based on the observation that studies showing an increase in adherence without an improvement in outcome provide no practical guidance for practice. The criterion of at least 6 months follow-up for long-term treatments was based on the premise that such interventions must have persistent effects if they are to be of practical clinical benefit.

Each potentially relevant full-text article was reviewed independently by at least 2 of the reviewers according to the criteria for review, reading until at least 1 exclusionary characteristic was found or until the end of the article, whichever came first. Disagreements about whether criteria were met (primarily assessment of confounding and adequacy of follow-up) were resolved by discussion. Eligible studies differed in venues, patient selection, clinical disorders, interventions, adherence measures, reporting, and outcome measures. Thus, there was insufficient

common ground for pooling differences between groups or calculating effect sizes that would permit quantitative summarization (ie, meta-analysis) of findings across studies. Methods for this systematic review have also been described in detail elsewhere.<sup>2</sup>

Because explicit criteria were used to select trials for our review, the studies included are quite homogeneous from a methodological perspective. Nonetheless, it is possible that there still exists a relationship between the methodological quality of the included studies and the success of their respective interventions. To test this hypothesis, we applied the 5-point Jadad Scale,<sup>11</sup> a widely used validated tool for assessing the methodological quality of RCTs, to all of our included studies, with 2 modifications. First, due to the nature of the interventions tested for adherence, blinding of the patient is essentially impossible. However, it is still possible to blind outcome assessors; therefore, for item 2 on Jadad's scale, we allotted 1 point to studies in which those assessing the adherence and clinical outcomes were blinded. Second, the importance of concealment of allocation in RCTs was demonstrated after publication of the Jadad Scale; therefore, we awarded an extra point to studies in which allocation was concealed. Fisher exact tests and univariate and multivariate logistic regression were used to compare study quality, based on the Jadad score, with success in achieving an improvement in adherence or clinical outcomes. All analyses were conducted with SPSS version 10.0 (SPSS Institute, Chicago, Ill) and  $P < .05$  was considered significant. Statistical analyses showed that there was no relationship between Jadad score and success in clinical or adherence outcomes.

We also hypothesized that interventions involving a greater number of components or categories, compared with interventions with fewer components or categories, would have greater success in improving adherence and clinical outcomes. Success in improving adherence or clinical outcomes was defined

as an improvement of at least 50% of the adherence or clinical outcomes that were measured in a particular study. Interventions for eligible studies were independently classified by 2 reviewers in at least 1 of 3 categories: behavioral, cognitive, or social/environmental,<sup>12</sup> and the number of components within each category was recorded. For example, an intervention consisting of written instructions and a reminder telephone call would be classified as having 2 components, with 1 component in each of the cognitive and behavioral categories. Because of the prior demonstration that patients with psychiatric disorders have lower adherence levels than those with other long-term disorders,<sup>5</sup> we also analyzed results with vs without those for psychiatric problems. Two-by-two tables were constructed for each study characteristic and adherence or clinical outcome. Unweighted Fisher exact tests and univariate and multivariate logistic regression were used to compare numbers and types of interventions with success in achieving an improvement in adherence or clinical outcomes. Because these analyses failed to show a relationship between the numbers and types of interventions and adherence or clinical outcomes, we opted to organize the description of studies according to the type of medical regimen (short-term vs long-term) and according to disease (within the categories of medical and psychiatric).

Our review was restricted to adherence with prescribed medications. Numerous other reviews refer to issues of adherence for various problems including obesity,<sup>13</sup> tuberculosis,<sup>14</sup> smoking,<sup>15-17</sup> and asthma.<sup>18</sup>

## RESULTS

Searches retrieved 6568 citations (including 101 review articles), 549 of which were judged to merit scrutiny of the full article. Some of the latter trials did not meet our inclusion criteria because of confounding, making it impossible to separate out independent effects of the interventions. Other reasons for exclusion included insufficient duration of follow-up, follow-up for less

than 80% of randomized patients, and measurement of adherence to medications that are not self-administered (ie, chemotherapy and vaccinations). Of the initial 549 trials, 34 citations<sup>19-52</sup> of 33 trials (with 1 study described twice<sup>29,52</sup>) met all review criteria. These trials tested 39 unconfounded interventions.

### Adherence Interventions

Many different interventions, alone and in combination, were tested with common themes such as more instruction for patients (oral and written material and programmed learning); increased communication and counseling (compliance therapy; automated telephone, computer-assisted patient monitoring and counseling; manual telephone follow-up; family intervention); various ways to increase the convenience of care (provision at the work-site, simplified dosing); involving patients more in their care through self-monitoring of their blood pressure, seizures, or respiratory function; reminders (tailoring the regimen to daily habits; special reminder pill packaging; dose-dispensing units of medication and medication charts; appointment and prescription refill reminders); and reinforcement or rewards for both improved adherence and treatment response (eg, reduced frequency of visits and partial payment for blood pressure monitoring equipment).

### Disorders Studied

A narrow range of disorders were targeted in the eligible trials. The most common conditions studied were hypertension (8 studies), schizophrenia or acute psychosis (8 studies), and asthma, chronic obstructive pulmonary disease, or both (5 studies). Other conditions included depression (2 studies), human immunodeficiency virus (2 studies), diabetes (2 studies), rheumatoid arthritis (1 study), epilepsy (1 study), and hyperlipidemia and cardiovascular disease (1 study). Only 3 eligible studies were of short-term conditions and all of these were acute infections.

### Interventions for Short-term Treatments

For short-term treatments (TABLE 1), Colcher and Bass<sup>25</sup> reported increased adherence with an antibiotic regimen for streptococcal pharyngitis with a relatively simple maneuver of counseling patients about the importance of full adherence, reinforced by written instructions. A second study<sup>32</sup> attempted to assess whether providing patients with information about adverse effects of their antibiotic treatment might cause lower adherence or increased perception of adverse effects; neither was found. Henry and Batey<sup>31</sup> found no significant improvements in adherence or rate of *Helicobacter pylori* eradication between patients receiving an intervention consisting of an information sheet on treatment, medication in dose-dispensing units, and a medication chart vs controls. However, adherence was very high in both groups and was likely stimulated by an initial 20-minute consultation given to all patients that emphasized the importance of adherence.

### Interventions for Chronic Conditions

Implementing changes in dosing schedules was the only relatively simple intervention that could be easily categorized (TABLE 2). The remaining interventions were generally too complex and multifaceted to categorize satisfactorily and were simply grouped by disease (TABLE 3). Because adherence rates are generally lower for patients with psychiatric conditions,<sup>5</sup> studies evaluating interventions for these disorders are presented separately (TABLE 4).

### Changes in Dosing Schedules for Long-term Regimens

Baird et al<sup>20</sup> reported significant improvements in adherence measured by pill count but no differences in urine drug levels or in blood pressure between patients receiving once-daily vs twice-daily metoprolol (Table 2).

Girvin et al<sup>28</sup> compared the effects of taking enalapril 20 mg once daily vs enalapril 10 mg twice daily for the treat-

ment of high blood pressure. Although a trend toward greater reduction in blood pressure occurred in the twice daily group, treatment outcomes were not significantly different. Furthermore, the adherence results are not considered because the follow-up was less than 6 months in duration (ie, the study was included because the results were negative for the clinical outcome).

Brown et al<sup>22</sup> reported improved medication adherence and treatment outcome in patients receiving controlled-release niacin twice daily vs regular niacin 4 times daily for the treatment of hyperlipidemia and coronary artery disease. This intervention would be generalizable to those situations where a reduction in the dosing fre-

quency is possible, while also maintaining the same total dose.

**Chronic Medical Conditions**

**Hypertension.** Sackett et al<sup>45</sup> reported no significant differences in adherence or clinical outcomes between hypertensive patients receiving care at the worksite from occupational health physicians, patients receiving programmed instructions about hypertension and adherence, or patients receiving a combination of both strategies (Table 3).

Two studies of complex intervention programs, involving provision of care at the worksite, special pill containers, counseling, reminders, self-monitoring, support groups, and feedback and reinforcement, reported positive effects on both adherence and

clinical outcomes in patients with hypertension.<sup>30,39</sup> The investigators for 1 of these studies provided evidence in another study that benefits outweighed costs.<sup>53</sup>

Becker et al<sup>21</sup> found no significant differences in adherence or blood pressure between patients receiving reminder medication packaging, in which all medicines taken together were packaged in a single plastic blister sealed with a foil backing on which was printed the days of the week and the time of day at which each medication was to be taken, and those receiving separate vials labeled with drug name, dosage, and instructions for each medication.

Friedman et al<sup>27</sup> tested a telephone-linked computer system for monitoring

**Table 1.** Interventions Aimed at Improving Medication Adherence for Short-term Regimens

Condition	Source	Intervention		Control		Clinical Outcome	Adherence Outcome
		Sample Size	Strategy	Sample Size	Strategy		
Streptococcal pharyngitis	Colcher and Bass, <sup>25</sup> 1972	100	Special counseling and written instructions on need to take all pills	100	Usual care	Throat culture* Relapse (results not reported)	Presence of drug in urine†
Acute infections	Howland et al, <sup>32</sup> 1990	50	Warnings about potential adverse effects of drugs	48	No warnings about adverse effects of drugs	Adverse effects‡	Mean pills/d‡ Patient reporting‡ Mean pills/40‡
<i>Helicobacter pylori</i> infection	Henry and Batey, <sup>31</sup> 1999	60	10 Days of omeprazole 20 mg twice daily, amoxicillin 500 mg three times daily and metronidazole 400 mg three times daily, oral advice on medication use, medication in dose-dispensing units, information sheet on treatment, medication chart, telephone call 2 days after the start of therapy	59	10 Days of omeprazole 20 mg twice daily, amoxicillin 500 mg three times daily and metronidazole 400 mg three times daily, oral advice on medication use and its possible adverse effects in an initial 20-minute consultation	Urea breath test (for <i>H pylori</i> presence)‡	Telephone interview and pill count‡

\*P≤.05.  
†P≤.005.  
‡Not significant at P = .05 level.

**Table 2.** Studies Implementing Changes in Dosing Schedules as a Strategy for Improving Medication Adherence

Condition	Source	Intervention		Control		Clinical Outcome	Adherence Outcome*
		Sample Size	Strategy	Sample Size	Strategy		
Hypertension	Baird et al, <sup>20</sup> 1984	196	Once-daily metoprolol	193	Twice-daily metoprolol	Blood pressure*	Pill count‡ Urine measurements
	Girvin et al, <sup>28</sup> 1999	27	Enalapril 20 mg once daily	27	Enalapril 10 mg twice daily	Blood pressure*	Pill count‡ Electronic monitoring‡
Hyperlipidemia and coronary artery disease	Brown et al, <sup>22</sup> 1997	31	Controlled-release niacin twice daily	31	Regular niacin 4 times/d	Target cholesterol level†	Pill count‡

\*Not significant at P = .05 level.  
†P≤.01.  
‡P≤.005.

**Table 3.** Interventions Aimed at Improving Medication Adherence for Chronic Medical Disorders\*

Source	Intervention		Control		Clinical Outcome	Adherence Outcome
	Sample Size	Strategy	Sample Size	Strategy		
<b>Hypertension</b>						
Sackett et al, <sup>45</sup> 1975	37	Care at worksite by occupational health physicians	25	Neither intervention	Blood pressure†	No. of tablets‡ Drugs in urine‡ Changes in serum chemistry‡
	28	Programmed instructions about hypertension and adherence				
	44	Both				
Haynes et al, <sup>30</sup> 1976	20	Tailoring, self-monitoring of pills and blood pressure, rewards for higher adherence and lower blood pressure	18	Usual care	Blood pressure†	Pill count‡
Johnson et al, <sup>33</sup> 1978	34	Self-monitoring of blood pressure at home	34	Neither intervention	Diastolic blood pressure†	Interview and pill counts‡
	33	Monthly home visits by a research assistant				
	35	Both				
Logan et al, <sup>39</sup> 1979	232	Worksite care by nurses, tailoring of medications to daily schedule, self-monitoring of blood pressure, rewards for higher adherence and lower blood pressure	225	Usual care at physician's office	Blood pressure§	Questionnaire and pill count
Becker et al, <sup>21</sup> 1986	86	Special reminder pill packaging	85	Separate vials for each medication	Blood pressure†	Patient self-report‡ Pill count‡
Friedman et al, <sup>27</sup> 1996	156	Telephone-linked computer system	145	Regular medical care	Blood pressure‡ Short-Form 36†	Home pill count‡
<b>Asthma</b>						
Bailey et al, <sup>19</sup> 1990	132	Pamphlet, workbook, counseling, telephone follow-up, support group	135	Instructional pamphlet	Severity of asthma symptoms   Bothered by asthma‡ Respiratory problems   Impact on life†	10-Item checklist for inhaler use   Self-report scales   Subjective health care scale
Cote et al, <sup>26</sup> 1997	45	Asthma education program, written self-management action plan, symptom monitoring	54	Basic disease information provided, oral action plan could be given by physician	Missed work† Hospitalization† Emergency department visits† Steroid use†	Weight of used canisters†
Gallefoss and Bakke, <sup>29</sup> 1999	39 Patients with asthma and 32 patients with COPD	Patient brochure, 2 group sessions (2 h), 1 or 2 individual sessions (40 min) from both a nurse and a physiotherapist, individual treatment plan on the basis of the acquired personal information and 2 wk of peak flow monitoring	39 Patients with asthma and 32 patients with COPD	Usual care from general practitioner	Forced expiratory volume in 1 s† Peak expiratory flow†	Percentage dispensed divided by prescribed†
Levy et al, <sup>38</sup> 2000	103	Asthma consultation (1 h) with study nurse, followed up by >2 consultations (30 min) at 6-wk intervals	108	Usual care	Peak flow   Symptom scores   Severe attacks† Days off work† Use of medical services‡	Adherence to self-management of moderate attacks† Adherence to self-management of severe attacks‡
van Es et al, <sup>48</sup> 2001	58	Discussion of "asthma management zone system" with pediatrician, 4 individual sessions with the asthma nurse, 3 educational group sessions with asthma nurse	54	Usual care, pediatrician every 4 mo	Forced expiratory volume in 1 s† Symptoms severity† Hospital admissions† Oral steroids†	Self-report† Physician estimate†

(continued)

**Table 3.** Interventions Aimed at Improving Medication Adherence for Chronic Medical Disorders\* (cont)

Source	Intervention		Control		Clinical Outcome	Adherence Outcome
	Sample Size	Strategy	Sample Size	Strategy		
<b>Diabetes</b>						
Piette et al, <sup>43</sup> 2000	137	Automated telephone assessment and self-care education calls with nurse follow-up	143	Usual care	HbA <sub>1c</sub> † Glucose   Diabetic symptoms	Self-reported adherence
Wysocki et al, <sup>49</sup> 2001	38	Behavioral-Family Systems Therapy (10 sessions), \$100 monetary incentive for attending all 10 sessions	41	Current therapy (standard pediatric endocrinology follow-up and self-management training)	HbA <sub>1c</sub> †	Self-care inventory‡
	40	Education and Support (10 group education and social support meetings), \$100 monetary incentive for attending all 10 sessions				
<b>Human Immunodeficiency Virus</b>						
Knobel et al, <sup>34</sup> 1999	60	Individualized counseling consisting of adaptation of treatment to patient's lifestyle and detailed treatment information	120	Conventional care	Viral load† Reduction in viral load‡ Increase in CD4 count†	Structured interview with pill count§
Tuldra et al, <sup>47</sup> 2000	55	Psychoeducative intervention, telephone number given should patients have any questions, oral reinforcement of adherence at follow-up visits	61	Usual medical follow-up	RNA levels†	Self-report†
<b>Rheumatoid Arthritis</b>						
Brus et al, <sup>23</sup> 1998	29	6-Group patient education meetings: 4 (2-h) meetings offered during the first months plus reinforcement meetings after 4 and 8 mo (partners were invited to attend the meetings)	31	Brochure on rheumatoid arthritis	Disease activity† Physical function†	Tablets prescribed divided by tablets obtained†
<b>Epilepsy</b>						
Peterson et al, <sup>41</sup> 1984	27	Counseling, leaflet, self-monitoring of pill taking and seizures, mailed reminders for appointments and missed drug refills	26	Usual care	No. of self-reported seizures†	Plasma anticonvulsant levels‡ Prescription refill§ Appointment follow-up†

\*COPD indicates chronic obstructive pulmonary disease; HbA<sub>1c</sub>, glycosylated hemoglobin.  
 †Not significant at P = .05 level.  
 ‡P ≤ .05.  
 §P ≤ .01.  
 ||P ≤ .005.

and counseling patients with hypertension. When adjusted for age, sex, and baseline adherence, the patients using the telephone-linked computer system demonstrated a greater improvement in medication adherence than those receiving usual care. Further adjustment for baseline blood pressure resulted in a significant improvement in diastolic blood pressure in the telephone-linked computer group but no difference between the groups for systolic blood pressure. Subgroup analysis showed that improvements in medication adherence and diastolic blood pressure were confined to

patients who were nonadherent at baseline (<10% of all patients).

**Asthma.** Bailey et al<sup>19</sup> reported positive effects on adherence and patient outcomes with a complex intervention for asthmatic patients. Patients in the intervention groups were provided with a standardized set of asthma information pamphlets; a skill-oriented, self-help workbook; a one-to-one counseling session; and additional adherence strategies such as an asthma support group and telephone calls from a health care educator. Patients in the control group were sim-

ply provided with the standardized asthma pamphlets.

Cote et al<sup>26</sup> studied a complex intervention involving an asthma education program, written self-management action plan, and symptom monitoring; this failed to improve medication adherence or clinical outcomes.

Gallefoss and Bakke<sup>29</sup> tested a complex intervention in patients with asthma and chronic obstructive pulmonary disease. This intervention consisted of a patient brochure and 2 group education sessions (2 hours each) with 1 session delivered by a physician and the other

by a pharmacist. In addition, 1 or 2 individual sessions (40 minutes) were supplied by a nurse and another 1 or 2 educational sessions (40 minutes) by a physiotherapist. At the final teaching

session the patients received an individual treatment plan and 2 weeks of peak flow monitoring. Gallefoss and Bakke<sup>29</sup> reported a statistically significant increase in the proportion of inter-

vention group asthma patients who collected at least 75% of prescribed steroid inhaler doses from the pharmacy compared with asthma controls, but the difference in adherence was not quite

**Table 4.** Interventions Aimed at Improving Medication Adherence for Psychiatric Disorders\*

Source	Intervention		Control		Clinical Outcome	Adherence Outcome
	Sample Size	Strategy	Sample Size	Strategy		
<b>Schizophrenia</b>						
Strang et al, <sup>46</sup> 1981	17	Family therapy	15	Individual supportive therapy	Relapse†	Need for intramuscular drugs‡ Tablet taking§ Drug levels‡
Xiong et al, <sup>50</sup> 1994	34	Family counseling and close follow-up	29	Prescription of medication without formal follow-up	Relapse (at 12† and 18‡ mo) Rehospitalization rate (at 12 and 18 mo)† Employment† Social dysfunction† Family social burden†	Nonhospitalized time for which the patient took more than 50% of the dosage prescribed at the time of last contact with a psychiatrist‡
Zhang et al, <sup>51</sup> 1994	42	Family intervention	41	Prescription of medication without formal follow-up	Hospitalization rate§ Hospital-free days§	>33% dose prescribed for >6 d/wk‡
Chaplin and Kent, <sup>24</sup> 1998	28	Individual semi-structured educational sessions	28	Usual care	Relapse‡ Increase in antipsychotic dose‡	Direct questioning plus case notes and depot card examination‡ Missing >2 wk of treatment‡
Merinder et al, <sup>40</sup> 1999	23	8-Session psychoeducational program for patients with schizophrenia and their relatives	23	Usual treatment provided in community psychiatry	BPRS‡ GAF‡	Case notes of medication use‡
Razali et al, <sup>44</sup> 2000	80	CMFT	86	BFT	BPRS† GAF‡ SBS‡ Rehospitalization‡ Family burden†	Interview plus unused medication
<b>Depression</b>						
Peveler et al, <sup>42</sup> 1999	53 52 53	Treatment information leaflet or Drug counseling or Both	55	Usual care	Depressive symptoms‡ Short-Form 36‡ Physician and hospital visits‡	Self-reported adherence‡
Katon et al, <sup>35</sup> 2001	194	Patient education, 2 visits with a depression specialist, telephone monitoring and follow-up	192	Usual care	Depressive symptoms¶ Relapse symptoms‡	Prescription refills   Meeting minimum dosing requirement
<b>Acute Psychosis</b>						
Kemp et al, <sup>36</sup> 1996	25	4-6 Sessions of compliance therapy	22	4-6 Sessions of nonspecific counseling	Global social functioning¶ Readmission¶ BPRS‡ GAF‡	Drug attitudes inventory¶ Nurse assessment¶
Kemp et al, <sup>37</sup> 1998	39	4-6 Sessions of compliance therapy	35	4-6 Sessions of nonspecific counseling	Global social functioning¶ Readmission¶ BPRS‡ GAF‡	Drug attitudes inventory¶ Nurse assessment¶

\*BPRS indicates Brief Psychiatric Rating Scale; GAF, Global Assessment of Function; CMFT, Culturally Modified Family Therapy; BFT, Behavior Family Therapy; and SBS, Social Behavior Schedule.

†Not significant at P = .05 level.

‡P ≤ .05.

§P ≤ .01.

||P ≤ .005.

¶Significance reported but P value not provided.

significant when based on median adherence. Furthermore, a flaw in the study design undermined the credibility of even these marginally positive results: participants assigned to the educational program but not attending all sessions were withdrawn.<sup>52</sup> Thus, the results for compliance were based on follow-up of 38 of 39 control participants but only 30 of 39 intervention participants (Fisher exact test, 2-tailed,  $P = .01$ ). Data obtained from the authors (F. Gallefoss, written communication, January 2002) on forced expiratory volume in 1 second outcomes for patients at 12 months follow-up indicated that there was a significant improvement for asthmatic intervention patients in forced expiratory volume in 1 second scores compared with the control. However, this statistical analysis was also based on per-protocol methods (including only those following the recommended protocol). This result was not considered as a clinical improvement because omitting noncompliers from the analyses clearly biases the results. Finally, there were no improvements in adherence or clinical outcomes for patients with chronic obstructive pulmonary disease, even based on the per protocol analysis.

Levy et al<sup>38</sup> reported that an intervention involving asthma education from hospital-based specialist asthma nurses improved adherence and clinical outcomes in asthmatic patients. Self-reported adherence was significantly higher in the intervention group for use of inhaled corticosteroids and rescue medication for severe asthmatic attacks, although there was no significant difference between the groups for use of these medications for mild attacks. Intervention patients also had significantly higher peak expiratory flow values and significantly fewer symptoms at 6 months than patients in the control group, accompanied by fewer days off work and fewer consultations with health care professionals.

Van Es et al<sup>48</sup> tested the effectiveness of a 1-year intervention involving individual instruction and review of asthma control from a pediatrician,

individual and group educational sessions with an asthma nurse, and written summaries of group sessions. At 12 months, there were no significant improvements in adherence to prophylactic medications or in clinical outcomes.

**Diabetes.** Piette et al<sup>43</sup> evaluated the effect of biweekly automated telephone assessment and self-care education calls with nurse follow-up on the management of diabetes. Patients were considered to have a problem with medication adherence if they reported that they "sometimes forget to take their medication," "sometimes stop taking their medication when they feel better," or "sometimes stop taking their medication when they feel worse." Compared with usual care, patients in the intervention group reported fewer problems with medication adherence. Patients in the intervention group also had lower glycosylated hemoglobin levels, lower serum glucose levels, and fewer diabetic symptoms than those in the control group.

Wysocki et al<sup>49</sup> compared Behavioral-Family Systems Therapy and Education and Support with current therapy for adolescents with diabetes. Behavioral-Family Systems Therapy included group instruction about diabetes and problem-solving training, communication skills training, cognitive restructuring, and functional and structural family therapy. Education and Support included group instruction about diabetes and social support but not family communication and communication skills. Patients from both groups also received a monetary incentive (US \$100) for attending all sessions. Behavioral-Family Systems Therapy resulted in an improvement in medication adherence at 6 and 12 months; however, had no effect on major clinical outcomes such as adjustment to diabetes or diabetic control. Education and Support was not associated with any improvements in adherence or clinical outcomes.

**Human Immunodeficiency Virus.** Knobel et al<sup>34</sup> reported significant improvements in adherence to highly active antiretroviral therapy (HAART) and

a significant reduction of viral loads in patients receiving individualized counseling vs patients receiving conventional care.

In another study targeting adherence to HAART, Tuldra et al<sup>47</sup> evaluated a psychoeducative intervention. Although statistically significant improvements were not found for adherence or clinical outcomes in the intention-to-treat analysis, improvements in compliance to HAART at 48 weeks and an increase in the proportion of patients with a viral load less than 400 copies/mL in the intervention group were observed when a per-protocol analysis was conducted. The lack of statistical significance observed using the intention-to-treat analysis may be a reflection of a low power to detect differences due to the relatively small sample size for each arm ( $n = 55$  for intervention,  $n = 61$  for control). A per-protocol analysis is suspect in any adherence study because it ignores patients who dropped out, which is the most severe form of nonadherence.

**Rheumatoid Arthritis.** Brus et al<sup>23</sup> evaluated an intervention involving patient education meetings focusing on compliance both with medication therapy and with a number of physical activities in patients with rheumatoid arthritis. The program was implemented in groups and partners were invited to attend the meetings. Patients receiving this intervention did not demonstrate any improvements in compliance or clinical outcomes compared with patients in the control group, who simply received a brochure on rheumatoid arthritis.

**Epilepsy.** Peterson et al<sup>41</sup> implemented a complex intervention involving counseling, disease and drug information leaflets, self-monitoring of medication adherence and seizures, mailed reminders for appointments, and missed drug refills for patients with epilepsy. Although significant improvements were observed for medication adherence and serum drug levels, significant effects were not observed for frequency of self-reported seizures or appointment follow-up.

### Psychiatric Disorders

Adherence interventions tested in patients with psychiatric disorders were organized into 4 broad categories: family therapy, compliance counseling for patients, patient education, or a combination of 2 or more of these (Table 4). The interventions studied were diverse in nature and therefore the groupings are simply intended to serve as a general guide. Overall, combination interventions and compliance counseling for patients appeared to be effective for improving clinical and adherence outcomes,<sup>35,37</sup> followed closely by family-oriented therapies, which were successful for both adherence and clinical outcomes in some cases,<sup>44,46</sup> and less successful in other studies.<sup>50,51</sup> The education-oriented interventions eligible for this review<sup>24,40,42</sup> were generally unsuccessful.

The most complex of the interventions involved combining patient education and counseling. Katon et al<sup>35</sup> tested an intervention in which patients received instruction (book and videotape), 2 visits to a depression specialist, 3 telephone visits (aimed at enhancing adherence to antidepressant medications, monitoring of symptoms, and development of a written relapse prevention plan), personalized mailings at 2, 6, 10, and 12 months, and telephone follow-up assessments at 3, 6, 9, and 12 months. Overall, intervention patients demonstrated significant improvements in adherence and depressive symptoms compared with patients receiving usual care.

Kemp et al<sup>37</sup> evaluated the effectiveness of a compliance counseling program in patients with psychotic disorders. Based on the 12-month data, patients receiving compliance therapy had higher adherence ratings and better social functioning than patients receiving nonspecific counseling. Furthermore, 6-month data indicated that patients receiving compliance therapy had significantly greater insight than those receiving nonspecific counseling.

Strang et al<sup>46</sup> found that family therapy, in which clinical staff worked closely with families of schizophrenic

patients, resulted in significant improvements in adherence and clinical outcomes compared with individual supportive therapy. Xiong et al<sup>50</sup> also compared family supportive care (monthly 45-minute counseling sessions) with usual care and reported a reduction in rehospitalization, relapse, social dysfunction, and family social burden, with an increase in employment in the family intervention group but found no significant differences in medication adherence. Zhang et al<sup>51</sup> demonstrated that, despite a lack of improvement in adherence, there was a significant effect of family therapy on preventing relapses among patients with schizophrenia.

In another study, Razali et al<sup>44</sup> compared the effects of culturally modified family therapy (intervention group) with behavioral family therapy (control group) in the management of schizophrenia. At 6 months and 1 year, patients in the intervention group had significantly higher adherence than those in the control group. At 1 year, patients in the intervention group also had significantly greater reduction of family burden, reduction in the number of exacerbated cases (according to Brief Psychiatric Rating Scale), and improvement in global assessment of functioning scores. Because 1 psychiatrist treated all the control patients, while a second psychiatrist treated all the intervention patients, the physicians' own styles are inseparable from the rest of the control and intervention treatment packages to which patients were randomized. Therefore, the generalizability of this study may be limited.

Chaplin and Kent<sup>24</sup> found that there was no significant difference in relapse rate or medication adherence in schizophrenic patients receiving individual, semi-structured educational sessions compared with patients receiving usual care. Merinder et al<sup>40</sup> found that an intervention consisting of family psychoeducation in patients with schizophrenia had no effect on improving adherence or on major clinical outcomes such as psychopathology or psychosocial functioning.

Peveler et al<sup>42</sup> compared the effects of treatment information leaflets, drug counseling, or a combination of both with usual care in patients suffering from depression. The treatment leaflets had no effect on adherence, depressive symptoms, or overall health care status. Although counseling resulted in a significant improvement in adherence and clinical outcomes, the results were not considered because the follow-up was less than 6 months in duration.

### Relationship Between Number and Type of Adherence Interventions

The median number of components used in an adherence intervention package was 3 (range, 1-6). The adherence intervention package was categorized as including behavioral, cognitive, or social aspects (62%, 74%, and 24%, respectively). None of the study intervention package characteristics (ie, used for psychiatric disorder, >1 component, >3 components, >1 category, use of behavioral category, use of cognitive category, use of social category) predicted improvement on adherence or clinical outcomes.

### COMMENT

We reviewed studies that assessed interventions designed to enhance medication adherence and that measured the interventions' effects on both medication adherence and health care outcomes. Forty-nine percent of the interventions tested (19 of 39 in 33 studies) were associated with statistically significant increases in medication adherence and only 17 reported statistically significant improvements in treatment outcomes. For short-term treatments (<2 weeks), 1 of 3 interventions (in 3 studies) resulted in improvements in adherence and clinical outcomes. For long-term treatments, 18 of 36 interventions reported in 30 trials were associated with improvements in adherence but only 16 interventions led to improvements in treatment outcomes. Major clinical outcomes such as death, blindness, or stroke were not assessed; the

studies evaluated intermediate outcomes such as blood glucose or blood pressure control. Almost all the interventions that were effective for long-term care were complex, including combinations of more convenient care, information, counseling, reminders, self-monitoring, reinforcement, family therapy, and other forms of additional supervision or attention. Even the most effective interventions did not lead to large improvements in adherence and treatment outcomes. We also failed to find a pattern of types or numbers of interventions that predicted success. Current methods of improving adherence for chronic health problems are mostly complex, labor-intensive (and thus expensive), and not predictably effective. Nevertheless, many intervention programs did lead to improved adherence and treatment success, and 1 study even documented cost-effectiveness.

The existing literature on interventions to improve patient adherence to self-administered medications has several limitations. First, studies of adherence that focus on patients who are willing to participate in research studies may be missing the key problems or beneficiaries of intervention, including those who have not sought care and those who have dropped out of care. In fact, the first task facing many physicians may be improving patient attendance at medical appointments. Macharia et al<sup>54</sup> found that telephone prompting, patient reminder letters, orientation statements, providing the patient with information about the reason for the appointment, clinic organization, and contracting with patients to acquire their formal agreement to attend future appointments improved attendance in both medical and psychosocial populations. However, this analysis focused on settings where appointment keeping ensured achievement of the intended health care objective such as screening procedures, referral for consultation, and appointments for counseling or administration of medications. Therefore, caution is warranted in extrapolating the results to settings where patients attend appointments for

ongoing care that is self-administered between visits.

Second, as only published studies were considered in the review, the findings are likely to overestimate the benefits of the interventions tested.<sup>55,56</sup> However, some studies may have underestimated intervention effects. As already noted, most of the measures of adherence were imprecise, often relying on self-report, a method that is known to overestimate adherence<sup>5,8,57</sup> that could easily blur any differences between groups, particularly in unblinded studies in which patients in an active control group might try to please the investigators. Also, although we selected only studies that measured both adherence and treatment outcome, the measures were not often objective and, when subjective, the assessors were sometimes aware of the study group of patients, increasing the possibility of biased assessments.

Furthermore, some interventions may work well but they were not tested well. For example, once or twice a day dosing may secure higher adherence than 3 or 4 times a day. However, 2 studies evaluating dosing frequency only compared once vs twice a day, finding a difference in adherence but not in clinical effects.<sup>20,28</sup> A study evaluating a wider range of dosing schedules failed to meet our inclusion criteria.<sup>58</sup> One study<sup>22</sup> comparing 2 vs 4 times per day dosing showed an improvement in medication adherence and in treatment outcome in the twice per day group. However, this study was completed by 29 men who had previously participated in a study investigating the regression of coronary artery disease as a result of intensive lipid-lowering therapy, and these patients may not represent those in usual care.

In addition, most of the studies had small numbers of patients and lacked power to detect clinically important effects. As a general guide, studies with a single intervention and control group would need to include at least 60 participants per group if they are to have at least 80% power to detect an absolute difference of 25% in the propor-

tion of patients judged to have adequate adherence. Only 11 of the 33 investigations to date have met this standard.\* Interestingly, significant improvements in both clinical and adherence measures were observed in the intervention group in 9 of 11 studies that were sufficiently powered, although a significant improvement in adherence but not clinical outcomes was reported in another study.

Most studies assessing successful complex interventions did not assess the separate effects of the components, begging the question of whether all elements were required. Furthermore, some authors did not adequately describe all parts of their interventions. For example, while the report might clearly describe that patients received reminders, the person or method of administering the reminder program was not described, or the role was described in some part of the text other than the section on intervention. In addition, most studies paid research staff to administer interventions, raising issues of generalizability to usual practice settings. This also raises the issue of attribution in many studies: if the control group received usual care, there would be no attention control in the study and any effects observed could be due to either the intervention proper or simply the nonspecific effects of increased attention paid to the intervention group.

Finally, none of the studies examined major clinical end points and the follow-up was relatively short-term in all, the longest being 24 months. Indeed, some studies demonstrated intervention effects on adherence and/or outcomes in the short-term but did not observe patients for a full 6 months, thereby failing to meet the eligibility criteria. Furthermore, most studies failed to assess adherence after the intervention had been discontinued, precluding assessment of the durability of the effect in studies with positive findings.

Although multifaceted interventions appear to be more effective than

\*References 19-21, 25, 27, 34, 35, 38, 39, 43, 44.

simple strategies for improving adherence and clinical outcomes, it is recommended that future studies of complex interventions attempt to elicit the effects of the individual components of the intervention in addition to the effect of the entire intervention as a whole. Each component of a complex intervention should be reported in sufficient detail. This would enable researchers to pinpoint the most effective aspects of complex interventions and to determine whether these aspects can be implemented alone or as part of the entire intervention package proposed. Also, future studies testing adherence interventions should use a minimum of 60 patients per study arm to achieve a satisfactory level of power. Ideally, objective clinically relevant outcomes should be used as the primary clinical end points and the study should be blinded at as many levels as possible. Finally, adherence outcomes should incorporate more objective measures such as electronic monitoring containers and blood or serum samples.

Because the results could be applied to any self-administered treatment, effective ways to help people follow medical treatments could have far larger effects on health care than any individual treatment. Low adherence to treatments has been associated with poor outcomes, even when the treatment was a placebo.<sup>10</sup> With the recent advances in medical therapeutics, studies of nonadherence and interventions to assist patients should flourish. However, the literature concerning interventions to improve adherence with medications remains surprisingly weak. Compared with the large amounts of trials for individual drugs and treatments, there are only a few relatively rigorous trials of adherence interventions. These provide little evidence that medication adherence can be consistently improved within the resources usually available in clinical settings or that this will lead predictably to improvements in important treatment outcomes.

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... the love of wilderness is more than a hunger for what is always beyond reach; it is also an expression of loyalty to the earth, the earth which bore us and sustains us, the only home we shall ever know, the only paradise we ever need—if only we had the eyes to see. Original sin, the true original sin, is the blind destruction for the sake of greed of this natural paradise which lies all around us—if only we were worthy of it. . . . No, wilderness is not a luxury but a necessity of the human spirit, and as vital to our lives as water and good bread. A civilization which destroys what little remains of the wild, the spare, the original, is cutting itself off from its origins, and betraying the principle of civilization itself.

—Edward Abbey (1927-1989)