Interventions for helping patients to follow prescriptions for medications (Review)

Haynes RB, McDonald H, Garg AX, Montague P

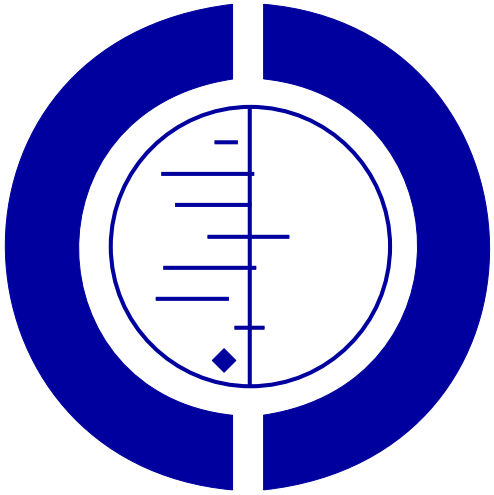

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TABLE OF CONTENTS

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This record should be cited as:
Haynes RB, McDonald H, Garg AX, Montague P. Interventions for helping patients to follow prescriptions for medications. *The Cochrane Database of Systematic Reviews* 2002, Issue 2. Art. No.: CD000011. DOI: 10.1002/14651858.CD000011.

This version first published online: 22 April 2002 in Issue 2, 2002.
Date of most recent substantive amendment: 08 February 2002

ABSTRACT

Background
People who are prescribed self-administered medications typically take less than half the prescribed doses. Efforts to assist patients with adherence to medications might improve the benefits and efficiency of health care, but also might increase its adverse effects.

Objectives
To update a review summarising the results of randomised controlled trials (RCTs) of interventions to help patients follow prescriptions for medications for medical problems, focusing on trials that measured both adherence and clinical outcomes.

Search strategy
Computerised searches to August 2001 in MEDLINE, CINAHL, The Cochrane Library, International Pharmaceutical Abstracts (IPA) PsychInfo, and Sociofile; bibliographies in articles on patient adherence; articles in the reviewers' personal collections; and contact with authors of original and review articles on the topic.

Selection criteria
Articles were selected if they reported an unconfounded RCT of an intervention to improve adherence with prescribed medications, measuring both medication adherence and treatment outcome, with at least 80% follow-up of each group studied and, for long-term treatments, at least six months follow-up for studies with positive initial findings.

Data collection and analysis
Information on study design features, interventions and controls, and results were extracted by one reviewer and confirmed by at least one other reviewer. The studies were too disparate to warrant meta-analysis.

Main results
For short-term treatments, one of three interventions reported in three RCTs showed an effect on both adherence and clinical outcome. Eighteen of 36 interventions for long-term treatments reported in 30 RCTs were associated with improvements in adherence, but only 16 interventions led to improvements in treatment outcomes. Almost all of the interventions that were effective for long-term care were complex, including combinations of more convenient care, information, reminders, self-monitoring, reinforcement, counselling, family therapy, and other forms of additional supervision or attention by a health care provider (physician, nurse, pharmacist or other). Even the most effective interventions did not lead to large improvements in adherence and treatment outcomes. Two studies showed that telling patients about adverse effects of treatment did not affect their adherence.

Authors' conclusions
The full benefits of medications cannot be realised at currently achievable levels of adherence. Current methods of improving adherence for chronic health problems are mostly complex and not very effective. Innovations to assist patients to follow medication prescriptions are needed.

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SYNOPSIS

Combinations of interventions such as more convenient care, reminders, reinforcement, and self-monitoring, can help people to follow prescriptions for medications

Many people do not take their medication as prescribed. The review considered trials of ways to help people follow prescriptions. For short-term drug treatments, counselling and written information helped. For longterm treatments, only some interventions led to improvements in health outcomes. They included combinations of more convenient care, information, counselling, reminders, self-monitoring, reinforcement, family therapy, and other forms of additional supervision or attention. Even with the most effective methods, improvements in drug use or health were not large. There is some evidence that telling people about adverse effects of drugs does not affect their use of the medications.

BACKGROUND

Adherence can be defined as the extent to which patients follow the instructions they are given for prescribed treatments. Thus, if a person is prescribed an antibiotic to be taken as one tablet four times a day for a week for an infection, but takes only two tablets a day for five days, their adherence would be (10/28=) 36%. The term, adherence, is intended to be non judgemental, a statement of fact rather than of blame of the patient, prescriber, or treatment. Compliance and concordance are synonyms for adherence.

Many reasons exist for non-adherence to medical regimens, including (but not restricted to) problems with the regimen (such as adverse effects), poor instructions, poor provider-patient relationship, patients' disagreement with the need for treatment or inability to pay for it. Assessing the evidence concerning reasons for low adherence is beyond the scope of this review; the interested reader is referred to other sources (e.g., Haynes 1979a; Houston 1997; Burke 1997).

Low adherence with prescribed treatments is very common. Typical adherence rates for prescribed medications are about 50% with a range from 0% to over 100% (Sackett 1979). To the extent that treatment response is related to the dose and schedule of a therapy, non-adherence reduces treatment benefits (Gordis 1979) and can bias assessment of the efficacy of treatments (Haynes 1979a; Haynes 1987a). With increasing numbers of efficacious self-administered treatments, the need is apparent for better understanding and management of non-adherence.

In previous reviews, we have examined the accuracy of clinical measures of non-adherence (Stephenson 1993), interventions to improve attendance at appointments for needed medical services (Macharia 1992), and interventions to enhance medication adherence (Haynes 1987b). In the latter review, some of the trials were confounded. For example, in one study (Bass 1986), interventions to increase medication adherence among patients with hypertension were inseparably combined with strategies to increase screening for this condition so that the independent effect of the medication adherence intervention could not be determined. Similarly, in another study (Jameson 1995), strategies to improve adherence to medication prescriptions were combined with modifications to the drug regimen preventing analysis of the independent contribution of each to the adherence and outcome effects. In this review, we have excluded confounded trials from consideration.

The current version of our review updates our 1998 version with 14 new studies (Brus 1998, Gallefoss 1999b (with supplementary information from Gallefoss 1999a; Girvin 1999; Henry 1999; Katon 2001; Knobel 1999; Levy 2000; Merinder 1999; Peveler 1999; Piette 2000; Razali 2000; Tuldra 2000; van Es 2001; Wysocki 2001). The interventions and findings of these studies do not substantively alter the conclusions of the previous version of the review. Of these 14 studies (evaluating 16 interventions), eight interventions were associated with significant improvements in at least one adherence measure at six months. Six of the studies demonstrated an improvement in at least one clinical outcome at six months, and there was an improvement in clinical outcomes at the 12 (but not six) month point for one additional study. It should be noted that the clinical improvements were seldom in the major clinical outcomes such as death, blindness or stroke; rather, the studies usually evaluated intermediate outcomes such as blood sugar or blood pressure control.

A range of disorders were evaluated in the 14 new studies. Two studies assessed acute disorders - acute asthma episodes (Levy 2000) and Helicobacter pylori infection (Henry 1999). The remaining 12 studies evaluated chronic conditions, including hypertension (Girvin 1999), asthma (Gallefoss 1999b; van Es 2001), chronic obstructive pulmonary disease (COPD) (Gallefoss 1999b), depression (Katon 2001; Peveler 1999), schizophrenia (Merinder 1999; Razali 2000), rheumatoid arthritis (Brus 1998), human immunodeficiency virus infection (HIV) (Knobel 1999, Tuldra 2000) and diabetes mellitus (Piette 2000; Wysocki 2001). Diabetes, HIV, depression and rheumatoid arthritis had not been assessed in articles meeting eligibility criteria for previous reviews.

In general, the interventions employed are very similar to those assessed in eligible studies from previous reviews. These interventions included changes in dosing schedule (i.e. once daily vs. twice daily (Girvin 1999), patient education from disease specialists (Brus 1998; Gallefoss 1999b; Katon 2001), disease consul-

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tations with specialist nurses (Levy 2000), individualized disease counseling and adaptation of treatment to patients' lifestyle (Knobel 1999), psycho educational programs (Merinder 1999; Tuldra 2000), drug information leaflets (Henry 1999; Peveler 1999), medication charts and special reminder packaging for medications (Henry 1999), automated telephone assessment and self-care education calls with nurse follow-up (Piette 2000), group sessions for education by nurses (Van Es et al 2001), and family-oriented disease management therapies (Razali 2000; Wysocki 2001).

Ethical standards for adherence research dictate that attempts to increase adherence must be judged by their clinical benefits, not simply their effects on adherence rates (NHLBI 1982). Accordingly, we included only studies in which both adherence and treatment effects were measured.

OBJECTIVES

In the current review, we sought to summarise all unconfounded randomised controlled trials of interventions to change adherence with prescribed medications in which both adherence and treatment effects were measured.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised controlled trials (RCTs) that provided unconfounded tests of interventions expected to affect adherence.

Types of participants

Patients who were prescribed medication for a medical (including psychiatric) disorder.

Types of intervention

Interventions of any sort intended to affect adherence with prescribed, self-administered medications.

Types of outcome measures

Original data concerning medication adherence, with at least 80% follow-up of participants, and with one or more measures of both medication adherence and treatment outcome. For long-term regimens, studies with initially positive findings were required to have at least six months follow-up from the time of patient entry; negative trials with shorter follow-ups were included on the grounds that initial failure was unlikely to be followed by success (Sackett 1979).

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

See: Consumers & Communication Group search strategy

Database searches for articles on adherence were completed by 15th August 2001, updating previous searches that were undertaken on 1st September 1993, 12th December 1993, 1st June 1994, 30th June 1995, 28th February 1997 and 31st July 1998. The search strategy of the MEDLINE, CINAHL and HEALTHSTAR database at each time was as follows: ((patient compliance (mh) OR patient adjacent to compliance (title and abstract) AND (clinical trials (pt) OR clinical trial (mh) OR all random: (textword)). An additional search strategy, first implemented in February 1997 was also replicated in July 1998: ((random: or control:) AND (patient compliance/ or patient dropouts/ or psychotherapy or treatment refusal/ or patient education/ or regimen:tw) AND (intervention:.tw. or outcome:.tw.) AND (medicat:.tw. or drug therapy)).

The PSYCHLIT search strategy was as follows: ((random or clinical or control or trial) AND (adherence or compliance or noncompliance or dropouts or patient education) AND (drug therapy or drug or medicat or treatment or regimen) AND (intervention or outcomes or treatment outcomes)).

The SOCIOFILE search strategy was as follows: ((patient or treatment or dropouts) AND (clinical trials or control) AND (drugs or medicine)).

The IPA search strategy was as follows: ((random? or clinical? or control?) AND (patient or adherence or treatment adherence or noncompliance or dropouts or medication compliance) AND (drug therapy or drug or medicat? or treatment or drug regimen or medical regimen) AND (intervention or outcomes)). An additional strategy incorporated into this IPA search involved the joining of all pairs of words with a (w). For example, treatment (w) adherence, drug (w) regimen.

The Cochrane Library search strategy was as follows: ((random*) AND (complian* or adheren* or pharmacotherapy or regimen* or educat*) AND (medicat*)); patient compliance; patient adherence; medication compliance.

An additional search, of the EMBASE database, was conducted for citations in any language, during the publication years 1997 through 1998, with the words appearing anywhere, using the following strategy: ((random* or control*) AND (patient compliance or patient dropouts or illness behavior or psychotherapy or treatment refusal or patient education or regimen*) AND (intervention* or outcome* or treatment outcome) AND (medicat* or drug therapy) AND (clinical trial or controlled study or randomized controlled trial)).

Authors of included trials were also contacted in November 1994, during winter 1997, in the summer of 1998, and in mid 2001 to suggest other published or unpublished trials that had been missed.

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METHODS OF THE REVIEW

Each full text article was reviewed independently by at least two of the reviewers according to the criteria for review (see Selection Criteria), reading until one or more exclusionary characteristics were found or until the end of the article, whichever came first. Articles were selected if they reported an unconfounded RCT of an intervention to improve adherence with prescribed medications, measuring both medication adherence and treatment outcome, with at least 80% follow-up of each group studied and, for long-term treatments, at least six months follow-up for studies with positive initial findings. Disagreements (primarily assessment of confounding and adequacy of follow-up) were resolved by discussion.

CONSUMER PARTICIPATION

No consumer referees were involved in the editorial process for the 1999 or 2001 update of this review.

DESCRIPTION OF STUDIES

The most recent searches of all sources retrieved a total of 1806 citations (including 11 review articles), 98 of which were judged to merit scrutiny of the full article; 15 of the latter met all review criteria (references as noted in Background), testing 16 unconfounded interventions in 14 trials. Thus, to date, searches have retrieved a total of 6568 citations (including 101 review articles), 549 of which were judged to merit scrutiny of the full article; 35 citations describing 33 trials (Logan 1981 provided supplementary cost-effectiveness information for the trial described in Logan 1979; Gallefoss 1999a providing supplementary information for the study described by Gallefoss 1999b) of the latter met all review criteria, testing 39 unconfounded interventions, including combinations of two of these interventions (Johnson 1978; Sackett 1975).

Key features of these 33 trials are summarised in the "Other Data" table. A narrow range of disorders was studied, with eight studies in hypertension, eight in schizophrenia or acute psychosis, five in asthma (and/or COPD), one in rheumatoid arthritis, one in epilepsy, one in hyperlipidemia and cardiovascular disease, two for depression, two for HIV, two for diabetes and only three for short-term conditions (acute infections in all cases). Diabetes, HIV, depression and rheumatoid arthritis had not been assessed in articles meeting eligibility criteria for previous reviews.

There were differences across studies in venues, clinical disorders, interventions, adherence measures and reporting, and outcome measures, so that there was not sufficient common ground for quantifying differences between groups or calculating effect sizes that would permit quantitative summarisation of findings across studies. Thus, the results of the studies are indicated in the "Other Data" table only as to whether there were statistically significant differences in adherence or treatment outcomes between the study groups being compared within studies. Unfortunately, as noted in the text descriptions of studies below, some of the negative results were unconvincing because of the small numbers of participants studied (ie, low statistical power).

METHODOLOGICAL QUALITY

Some trials or arms of trials did not meet our criteria because of confounding (see Excluded Trials list). For example, in one study (Colcher 1972), two groups received the same prescription for phenoxymethyl penicillin, but different instructions, providing an unconfounded comparison for the instructions, but a third group in the same trial received a different drug (penicillin G benzathine) by a different route (intramuscularly) with a different dose (1.2 million units) and schedule (one dose), making it impossible to separate out independent effects. Thus, only the unconfounded comparison of instructions for phenoxymethyl penicillin was included in the review.

None of the studies from previous reviews clearly dealt with "concealment of allocation", preventing investigators from anticipating and influencing which group their patient might be allocated to, although Friedman (Friedman 1996) used a paired randomization protocol, Bailey (Bailey 1990) did mention using envelopes (not stated to be opaque), and Haynes (Haynes 1976) claimed that the method of minimisation that they used was "immune to experimental bias." Four of the newly-identified studies, however, reported attempts to conceal allocation. Levy 2000 used a computer-generated randomisation scheme and claimed that the nurses had no idea which group the patients would be randomized into. Peveler 1999 stated that to maintain blinding their randomization key was concealed from interviewers (although it is somewhat unclear in this case whether randomisation was actually concealed from those enrolling patients). Piette 2000 implemented randomisation based on a table of randomly permuted numbers, stating that neither providers, research staff, nor prospective patients had knowledge of group assignment until patients had consented to participate. Finally, van Es (van Es 2001) mentioned that the principal investigator, who was not involved in selection and inclusion of patients, prepared numbered, opaque envelopes containing the treatment allocation.

None of the studies adjusted for multiple comparisons, although one (Bailey 1990) mentioned that "none of the outcomes for significance would have changed if adjustment for multiple comparisons had been made". It bears mentioning, however, that most of the studies had clearly stated primary analyses and only two or three statistical challenges of the data. Further, most of the studies reported no effect of interventions on patient outcomes and suffered not from the hazards of multiple comparisons, but rather from those of low power to detect potentially clinically important effects on patient outcomes.

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RESULTS

Many different interventions were tested with common themes such as more instruction for patients (verbal and written material (Becker 1986; Brus 1998; Colcher 1972; Cote 1997; Gallefoss 1999b; Henry 1999; Katon 2001; Levy 2000; Merinder 1999; Peveler 1999; van Es 2001) and programmed learning (Sackett 1975)); counselling (compliance therapy (Kemp 1996; Kemp 1998; Razali 2000; Tuldra 2000; Wysocki 2001); automated, telephone, computer-assisted patient monitoring and counselling (Friedman 1996; Piette 2000); manual telephone follow-up (Katon 2001), family intervention (Merinder 1999; Razali 2000; Strang 1981; Xiong 1994; Zhang 1994); various ways to increase the convenience of care (provision at the worksite (Sackett 1975; Haynes 1976; Logan 1979; Logan 1981), simplified dosing (Baird 1984; Brown 1997a; Girvin 1999); involving patients more in their care through self-monitoring of their blood pressure (Haynes 1976; Logan 1979), seizures (Peterson 1984), or respiratory function (Bailey 1990; Cote 1997); reminders (tailoring the regimen to daily habits (Sackett 1975; Haynes 1976; Logan 1979; Knobel 1999), special 'reminder' pill packaging (Becker 1986), dose-dispensing units of medication and medication charts (Henry 1999), appointment and prescription refill reminders (Peterson 1984); and reinforcement or rewards for both improved adherence and treatment response (eg reduced frequency of visits and partial payment for blood pressure monitoring equipment (Haynes 1976).

Just under half of the interventions tested (19 of 39; one short-term treatment and 18 long-term treatments) in the 33 studies were associated with statistically significant increases in medication adherence and only 17 reported statistically significant improvements in treatment outcomes (one short-term treatment and 16 long-term treatments). Most of the studies were quite small, however, and the possibility of a false-negative (beta) error is quite high.

Some interventions were highly complex and it is unlikely that their effects were mediated solely through changes in medication adherence. For example, in the study by Logan (Logan 1979), specialised nurses provided both adherence interventions and treatment adjustments to improve blood pressure control among patients with hypertension. Zhang and colleagues (Zhang 1994) also demonstrated that there was an effect of family therapy that was independent of increased medication adherence in preventing relapses among patients with schizophrenia. These studies may be confounded, and thus ineligible for our review, but the details of the interventions are not clearly enough described to determine if this is the case.

The generalisability of several interventions was unclear. For example, two studies from China among patients with schizophrenia (Strang 1981; Xiong 1994) tested an intensive intervention of clinical staff working closely with families, compared with providing control patients with 'usual care'. 'Usual care' was a prescription for two to three months of medication and then leaving patients to their own resources, including the decision of whether or not to seek follow-up care. It would be difficult to generalise the findings of these studies to settings in which either usual care was more vigorous, or the intensive intervention was not feasible.

Two studies of hypertension that reported positive effects on both adherence and patient outcomes (Haynes 1979a; Logan 1979) had, perhaps, the most intensive interventions, including care provided at the worksite, special pill containers, counselling, reminders, self-monitoring, support groups, feedback and reinforcement, all administered by staff who were supported from study funds. This raises the question of whether the interventions would be cost-effective in usual settings. Fortunately, the investigators for one of these studies went on to provide evidence that benefits outweighed costs (Logan 1981).

Another study in hypertensive patients (Friedman 1996) tested a telephone-linked computer system (TLC) for monitoring and counselling patients. The unadjusted results did not demonstrate significant improvement in compliance or clinical outcome in patients using TLC as compared to those patients receiving usual care. However, when the data were adjusted for age, sex, and baseline adherence, the patients using TLC demonstrated a greater improvement in medication adherence than those receiving usual care ($p<0.05$). Further adjustment, for baseline blood pressure, resulted in a significant improvement in diastolic blood pressure in the TLC group ($p<0.05$) but no difference between the groups for systolic blood pressure. Sub-group analysis showed, in people who were non-adherent at baseline (n=26), patients using TLC had greater improvement in medication compliance ($p<0.05$) and diastolic blood pressure ($p<0.05$) than those receiving usual care. In people who were adherent at baseline (n=241), TLC did showed no significant improvement in adherence with the use of TLC.

Piette (Piette 2000) evaluated the effect of biweekly automated telephone assessment and self-care education calls with nurse follow-up on the management of diabetes. Compared with usual care, patients in the intervention group reported fewer problems with medication adherence ($P < 0.003$). Patients in the intervention group also had lower glycated hemoglobin levels, lower serum glucose levels and fewer diabetic symptoms than those in the control group.

Another fairly complex intervention resulted in improvements in adherence and depression symptoms (Katon 2001). In this study, medication adherence and depressive symptoms were improved through a programme involving patient instruction (book and videotape), two visits to a depression specialist, three telephone visits over a period of one year (aimed at enhancing adherence to antidepressant medications, monitoring of symptoms and development of a written relapse prevention plan), four personalized mailings at two, six, 10 and 12 months, and telephone follow-up assessments at three, six, nine and 12 months. Patients in the intervention group had greater adherence to adequate dosage of

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antidepressant medication and were significantly more likely to refill medication prescriptions during the 12 month follow-up period. Patients in the intervention group also had significantly fewer depressive symptoms, but did not have fewer episodes of relapse or recurrence of depression.

In another study (Cote 1997), a more complex intervention did not improve adherence with medications to manage asthma. The intervention did result in an increase in asthma knowledge scores over the course of the study, but had no effect on the associated asthma morbidities. In contrast, a newly-identified study (Levy 2000) reported that a similar intervention involving asthma education from hospital-based specialist asthma nurses improved adherence and clinical outcomes in asthmatic patients. Self-reported compliance was significantly higher in the intervention group for use of inhaled topical steroids and rescue medication for severe asthmatic attacks, but there was no significant difference between the groups for use of these medications for mild attacks. In terms of clinical outcomes, intervention patients had significantly higher peak expiratory flow (PEF) values and significantly fewer symptoms at six months than patients in the control group. Furthermore, patients in the intervention group had fewer days off work and fewer consultations with health professionals.

Van Es (van Es 2001) tested the effectiveness of a one-year intervention involving individual instruction and review of asthma control for the prior two weeks 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 such as lung function, severity of asthma, or morbidity variables for patients in the intervention group. (There was evidence of a significant improvement in self-reported adherence at 24 months for the intervention group, but the follow-up at this point was <77%.)

Other educational interventions were not successful in improving compliance or clinical outcomes. Merinder (Merinder 1999) found that an intervention consisting of family psycho education (eight didactic interactive sessions) in schizophrenic patients had no effect on improving adherence or a number of clinical outcomes such as psychopathology, psychosocial functioning, or insight into psychosis. There was evidence of some effect on disease knowledge and patient satisfaction, but overall the intervention had no effect on adherence or major clinical endpoints. It is important to note, however, that this study was of very small sample size, and thus the power to detect improvements in adherence or clinical outcomes is very low.

Similarly, Brus (Brus 1998) evaluated an intervention involving six patient education meetings focusing on compliance with both medication therapy and a number of physical activities in patients with rheumatoid arthritis. Four two-hour meetings were offered during the first months of the intervention, and reinforcement meetings were given after four and eight months. Patients made contracts with themselves concerning their intentions. This 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. The sample size of this study was also small and thus, once again the power to detect improvements in adherence or clinical outcomes was very low.

Gallefoss & Bakke (Gallefoss 1999b, Gallefoss 1999a) tested another educational intervention in patients with asthma and COPD. This intervention consisted of a specially constructed patient brochure, two two-hour group sessions (separate groups for asthmatics and patients with COPD) concentrating on pathophysiology, anti obstructive medication, symptom awareness, treatment plans, and physiotherapy, with one session delivered by a physician and the second by a pharmacist. In addition, one or two 40-minute individual sessions were supplied by a nurse and another one or two 40-min educational sessions by a physiotherapist. The patient's pulmonary symptoms were registered and discussed with emphasis on the early symptoms experienced at exacerbations. The individual factors causing attacks/exacerbations and concerns regarding adverse effects of medication were discussed and inhalation technique was checked. At the final teaching the patients received an individual treatment plan on the basis of the acquired personal information and two weeks of peak flow monitoring. The authors reported a statistically significant increase in the proportion of intervention group asthma patients who collected at least 75% of prescribed steroid inhaler doses from the pharmacy, compared with asthma controls ($p<0.04$), but the difference in adherence wasn't quite significant when based on median adherence ($p=0.08$). Unfortunately, a fatal flaw in the study design undermines the credibility of even these marginally positive results: participants assigned to the educational program but not attending all sessions were withdrawn from the study (Gallefoss, Bakke and Kjaersgaard, 1999). Thus, the results for compliance were based on follow-up of 38 of 39 control group participants but only 30 of 39 intervention group participants (2P=0.014, Fisher's Exact Test). Data obtained via personal contact with the authors on FEV1 outcomes for patients at 12 months follow-up indicated that there was a significant improvement for asthmatic intervention patients in FEV1 scores compared with the control group. However, this statistical analysis was also based on per protocol methods (ie, including only participants who followed the study protocol), and therefore this result was not considered as a clinical improvement for the purposes of our review. Furthermore, the sample size of this study was relatively small and thus, once again the power to detect improvements in adherence or clinical outcomes is very low. Finally, there were no improvements in adherence or clinical outcomes for patients with COPD, even based on the per protocol analysis.

Another study evaluating educational interventions (Peveler 1999) compared the effects of treatment information leaflets, drug coun-

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selling or a combination of both to usual care in patients suffering from depression. The treatment leaflets had no effect on adherence, depressive symptoms or overall health status. This study was only 12 weeks in duration, which is shorter than our six months follow-up criterion. However, because the results were negative for adherence and clinical outcomes with the leaflet intervention, the paper was included for this review. (Counselling about drug treatment did result in a significant improvement in adherence and clinical outcomes. Nonetheless, because the follow-up was less than six months in duration, the results for counselling are not considered in the conclusions of this review.)

Kemp (Kemp 1998) reported 18-month follow-up data on the effectiveness of 'compliance therapy' ("a brief pragmatic intervention targeting treatment adherence in psychotic disorders, based on motivational interviewing and recent cognitive approaches to psychosis") in patients with psychotic disorders. Unfortunately, 35% of patients were lost to follow-up at this time. At 12 months, however, certain data were collected on more than 80% of patients. Patients receiving 'compliance therapy' demonstrated better social functioning ($p< 0.001$) and received higher adherence ratings ($p<0.001$) than those patients receiving non-specific counselling. However, there was no difference between the two groups for performance on the Brief Psychiatric Rating Scale. Only six-month data was available on insight, showing patients who received compliance therapy had significantly greater insight ($p<0.05$) than those receiving non-specific counselling.

Razali (Razali 2000) compared the effects of culturally modified family therapy (CMFT) with behavioral family therapy (BFT), both delivered by a psychiatrist, in the management of schizophrenia in a university hospital in West Malaysia. At six months and one year, patients in the intervention group (CMFT) had significantly higher compliance than those in the control (BFT) group. At one year, patients in the CMFT also had significantly greater reduction of family burden, reduction in number of exacerbated cases (according to BPRS scale), and improvement in global assessment of functioning (GAF) scores. The generalisability of this study may be limited as one psychiatrist treated all the control patients, while a second psychiatrist treated all the intervention patients. Further, it is possible that the therapist himself may be a factor in the outcomes reported in this study and thus must be considered part of the intervention and control procedure.

In another study evaluating a psycho educative intervention ("primarily to improve patients' knowledge and customs in handling medication to increase self-efficacy"), Tuldra (Tuldra 2000) assessed effects among HIV patients prescribed highly active antiretroviral therapy (HAART). In an intention to treat (ITT) analysis, no improvements were found in adherence or clinical outcomes (the p-values were slightly above the 0.05 significance level). However, when a per protocol analysis was conducted, the intervention resulted in 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. The lack of statistical significance observed using the ITT 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). The per protocol analysis is suspect in any adherence study as it ignores patients who dropped out, the most severe form of non adherence.

Knobel (Knobel 1999) reported significant improvements in compliance to highly active antiretroviral therapy and significant reduction of viral loads in patients receiving individualized counselling involving detailed information about drug therapy and adaptation of treatment regimens to suit the patient's lifestyle.

Wysocki (Wysocki 2001) reported six and 12-month follow-up data for the comparison of Behavioral-Family Systems Therapy (BFST) and Education and Support (ES) with current therapy for adolescents with diabetes. BFST included group instruction about diabetes and "problem-solving training, communication skills training, cognitive restructuring and functional and structural family therapy". ES included group instruction about diabetes and social support but not family communication and communication skills. BFST and ES patients received a monetary incentive ($100) for attending all sessions. Although not evident immediately post-treatment, BFST resulted in an improvement in medication adherence at six and 12 months. However, BFST had no effect on major clinical outcomes such as adjustment to diabetes or diabetic control, and ES was not associated with any improvements in adherence or clinical outcomes. Again, it should be noted that the sample size in this study was relatively small (BFST: n=38, ES: n=40, current therapy: n=41), thus limiting the power of the study.

Brown (Brown 1997a) tested controlled-release niacin, twice daily, versus regular niacin, four times daily, in the treatment of hyperlipidemia and coronary artery disease. Both medication adherence and treatment outcome were improved. Compliance was 95% with the controlled-release niacin versus 85% with regular niacin ($p<0.001$). There was a significant improvement in the lipid profile in the group using controlled-release niacin versus regular niacin ($p<0.05$). The controlled-release niacin was associated with fewer episodes of flushing than the regular niacin and this may have contributed to the increase in adherence and thus the better outcome. This intervention would be generalisable to those situations where a reduction in the dosing frequency is possible, while maintaining the same total dose.

In a study identified in the most recent review, Girvin (Girvin 1999) tested enalapril 20 mg once daily versus enalapril 10 mg twice daily in the treatment of high blood pressure. In this crossover study, overall medication adherence was improved, but treatment outcomes were not. The difference in percentage of doses taken by pill count between the two periods was significant in favour of the once daily regimen at $p<0.01$, the percentage of doses taken as measured by a pill container that recorded lid openings (MEMS) was significant in favour of once daily regimen at p<

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0.001, and the percentage of days with the correct number of doses taken was significant in favour of the once daily regimen at P <0.01. As a corollary, the percentage of days when no doses were taken was also significantly higher in the once daily regimen (P< 0.01). For treatment outcomes, there was a greater reduction in blood pressure, which almost reached statistical significance, in the twice daily group. This study did not have a 6-month follow-up period (only 16 weeks long). However, because the results were negative for the blood pressure outcomes, it qualifies for this adherence review. It should also be noted that this study was small in sample size (n=27) and may not be of sufficient power to detect improvements in clinical outcomes.

For short-term treatments, a study testing an intervention to increase adherence with a regimen for streptococcal pharyngitis (Colcher 1972) reported success with a relatively simple manoeuvre of counselling patients about the importance of full adherence, reinforced by written instructions. A second study in an acute setting (Howland 1990) attempted to assess whether providing patients with information about adverse effects of their antibiotic treatment might cause harm. Fortunately, no harm was found for either adherence or experiences of adverse effects. In a similar vein, but for longer term treatments, a study (Chaplin 1998) tested whether or not educating schizophrenic patients about benefits and adverse effects of their treatments, including tardive dyskinesia, decreases compliance with antipsychotic medications. Results showed no significant differences between study and control patients in terms of medication compliance or clinical deterioration. With 28 patients per group in this study, the power to detect a difference in adherence or relapse was low.

Henry (Henry 1999) evaluated an intervention consisting of an information sheet on H. Pylori treatment, medication in dose-dispensing units, and a medication chart for patients receiving medication for H. Pylori eradication. There were no significant improvements in compliance or rate of H. Pylori eradication between the intervention and control groups. It is important to note, however, that adherence to therapy was very high in both groups, thus precluding the need for any additional intervention. It is likely that the initial 20-minute consultation given to all patients emphasized the importance of compliance to the antibiotic therapy enough to induce almost complete adherence to the 10-day treatment course, and that any additional adherence procedures would therefore not produce any additional benefit.

DISCUSSION

Most people do not follow self-administered medical treatments as prescribed. The benefits from such treatments are diminished according to the degree of non-adherence and the efficacy of the treatments (Sackett 1979).

With the astonishing advances in medical therapeutics during the past two decades, one would think that studies of the nature of non-adherence and the effectiveness of strategies to help patients overcome it would flourish. On the contrary, the literature concerning interventions to improve adherence with medications remains surprisingly weak. Compared with the many thousands 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 improved consistently, within the resources usually available in clinical settings, and that this will lead predictably to improvements in treatment outcomes.

Indeed, as only published studies were considered in the review, these findings are likely to overestimate the benefits of the interventions tested to date (Dickersin 1992; Easterbrook 1991). Furthermore, many of the adherence interventions for long-term medications were exceedingly complex and labour-intensive. It is therefore difficult to see how they could be carried out in non-research settings, particularly under the current pall of cost-containment and staff reductions.

On the other hand, some studies may have underestimated intervention effects. Most of the measures of adherence were imprecise, often relying on self-report, a method that is known to overestimate adherence (Gordis 1979; Stephenson 1993; Haynes 1980) and that could easily blur any differences between groups.

Further, some interventions may work well, but they were not tested well. For example, once or twice a day dosing may secure higher adherence than three or four times a day. However one study looking into dosing frequency only compared once versus twice a day, finding a difference in adherence but not in clinical effects (Baird 1984). A study looking into a wider range of dosing schedules failed to meet our inclusion criteria (Echt 1991). More recently, a study comparing two versus four times per day dosing (Brown 1997a) 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 trial 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.

As a general guide, studies with a single intervention group 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 proportion of patients judged to have adequate adherence. The study group numbers in the Table show that only 11 of the 33 investigations to date have met this standard, so most studies lacked power to detect clinically important effects. For example, in a study of 38 patients (Haynes 1976), there was a significant increase in adherence associated with the intervention and an interesting within-group reduction of blood pressure of 5.4 mm Hg ($p < 0.001$) in the intervention group. However, the difference between the intervention and control groups for blood pressure change was not statistically significant (3.5 mm Hg, $p = 0.12$). In another example (Chaplin 1998), no significant

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differences were found for medication adherence or clinical outcome. However, there were fewer than 30 patients in each group, and the study is under-powered. In still another study reporting no improvement in either compliance or clinical outcome (Cote 1997), there were two intervention groups and one control group and each of the groups contained fewer than 60 people. This study is clearly under-powered. Newly-identified studies for this current review that also suffer from low power due to small sample size include Brus 1998; Girvin 1999; Gallefoss 1999a; Henry 1999; Merinder 1999; Peveler 1999; Tuldra 2000; van Es 2001 and Wysocki 2001.

It is important to note that our review is focused on interventions to increase medication adherence, excluding studies that reported only on reducing drop-out rates and missed appointments. An earlier review shows that adherence with appointments for medical care can be enhanced by a number of strategies (Macharia 1992). Patients dropping out of care are unlikely to be receiving any medication, and if those in care average about 50% adherence, keeping patients in care is arguably the most important adherence intervention at present. This assumes, however, that those who are prevented from dropping out, or who are returned to care by intervention, assume medication adherence rates that are sufficient to achieve clinically important benefits. This merits further testing.

Several commentators on this review have remarked on the negative message it conveys. They have suggested that the findings would not have been so discouraging, perhaps, had we included studies that measured only adherence. Certainly, investigators who seek to advance the methods for enhancing adherence would do well to look into studies that did not meet our criteria for measurement of both adherence and clinical outcomes. However, this criticism does not pertain to the purpose of this review which is to determine whether adherence interventions make a difference to clinical care outcomes. It simply cannot be assumed that measures to increase adherence do more good than harm even if they increase adherence. By analogy, the enthusiasm engendered by certain drugs that reduced cardiac arrhythmias in patients with unstable heart rhythms following myocardial infarction turned to dismay when more important clinical outcomes were assessed: these drugs decreased arrhythmias, but also increased mortality (CAST Trialists 1992; Echt 1991). Adherence is a process measure, a means to an end. Interventions to increase adherence consume resources and attempts to increase adherence can have adverse effects (loss of privacy and autonomy; increased adverse effects of treatments if taken in higher doses and so on).

Most studies assessing successful complex interventions did not assess the separate effects of the components, begging the question of whether all elements were required. Johnson and colleagues (Johnson 1978) attempted to address this question among hypertensive patients by studying the separate and combined effects of a more complex intervention including self-monitoring of blood pressure and home visits from study staff. Unfortunately, there were no measurable benefits even from the combined interventions.

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. Most studies paid research staff to administer interventions, raising issues in generalisability 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 non-specific effects of increased attention paid to the intervention group.

Although we only selected 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.

None of the studies examined major clinical endpoints. The follow-up was relatively short-term in all, the longest being 24 months. Indeed, some studies demonstrated intervention effects on adherence and/or outcome in the short-term, but did not observe patients for a full six months, thereby failing to meet the eligibility criteria for this review (eg Goodyer 1995; Rimer 1987). Further, 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. Thus, there are many shortcomings in the research to date.

Despite extensive searching, it is quite possible that we missed some trials that met all of our criteria. The literature on patient adherence is not well indexed because the number of studies is quite small and because it is scattered across traditional disease boundaries. We invite readers to send us any studies, published or unpublished, that may meet our criteria.

Our review is quite narrow in its focus, being restricted to prescribed medications and to studies that assessed both adherence and treatment outcomes. Numerous other reviews in the Cochrane Database of Systematic Reviews (CDSR) refer to issues of adherence. Reviews with a major focus on adherence include Harvey 1999 on obesity; Volmink 1999 on tuberculosis; Lumley 1999, Lancaster 1999, Silagy 1999 and many others on smoking; and Gibson 1999 on asthma.

AUTHORS' CONCLUSIONS

Implications for practice

Simpler treatment regimens can sometimes improve adherence and treatment outcomes for both short- and long-term treatments.

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Several complex strategies, including combinations of more thorough patient instructions and counselling, reminders, close follow-up, supervised self-monitoring, and rewards for success can improve adherence and treatment outcomes. However, these complex strategies for improving adherence with long-term medication prescriptions are not very effective despite the amount of effort and resources they consume.

Perhaps the most important single intervention, given its simplicity and effectiveness, is recalling patients who miss appointments, making every effort to keep them in care.

There is no evidence that low adherence can be "cured". Thus, efforts to improve adherence must be maintained for as long as the treatment is needed.

Implications for research

To achieve the full benefits of current medical therapies, we need further innovation in treatment methods themselves (preferably cures, or perhaps implantable treatments with minimal adverse effects); or better understanding of adherence, or unexpectedly positive findings from continued testing of permutations and combinations of the adherence intervention strategies tested to date.

Important innovations are more likely to occur if investigators join across clinical disciplines to tackle the problem. There is little evidence that low adherence with medications is disease- or regimen-specific, with the possible exception of psychiatric disorders (Haynes 1979).

As low adherence affects all self-administered treatments, and as the numbers of efficacious, self-administered treatments continue to grow, investment in fundamental and applied adherence research is likely to pay large dividends. The largest trial reported here had fewer than 500 patients and none of the trials sought effects on major morbidity or mortality. These smaller studies may be appropriate until an innovation appears to have clinically useful effects. At that point, the innovation should be tested in more substantial trials to document effects on clinically important outcomes (including adverse effects), feasibility in usual practice settings, and durability.

Because the results could be applied so broadly, effective ways to help people follow medical treatments could have far larger effects on health than any treatment itself. This is particularly so as low adherence to treatments has been associated with poor outcomes, even when the treatment was a placebo (Haynes & Dantes 1987).

ACKNOWLEDGEMENTS

Our thanks to Victor Montori, MD, Mayo Medical School, Rochester MN, for assisting with the translation of Knobel 1999. This review has benefited greatly from suggestions from external reviewers and we thank them for their advice.

POTENTIAL CONFLICT OF INTEREST

None.

SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- Health Information Research Unit, McMaster University, Hamilton, Ontario CANADA

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* *Indicates the major publication for the study*

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TABLES

Characteristics of included studies

Study	Bailey 1990
Methods	Random allocation by sealed envelope technique. Blinding of patients or staff to the experimental treatment that individual patients were receiving was not performed, however, contacts/care givers of control patients were kept separate from those of the intervention group.
Participants	Patients meeting the following diagnostic criteria were included in the study: recurrent episodes of wheezing or dyspnea, objective evidence of significantly increased airflow resistance during episodes, objective evidence of improvement in airflow when symptom free. Patients excluded from the study were those less than 18 years of age, those who refused to participate, or those with another pulmonary or severely debilitating disease that may have confused result interpretation.
Interventions	Patients randomised to the control or usual care group were provided with a standardised set of asthma pamphlets which contained comprehensive information about asthma. No special steps, however, were taken to ensure that patients actually read the pamphlets, and no special counselling, support groups, or systematic encouragement beyond routine physician encouragement were provided. While patients in the interventional self-management group were also provided with the standardised asthma pamphlets, they in addition were provided with a skill-oriented self-help workbook, a one-to-one counselling session, and were subject to several adherence-enhancing strategies, such as attending an asthma support group and receiving telephone calls from a health educator. Physicians emphasised these skills at regular clinic visits. A standard protocol for classifying patients in terms of level of severity and for relating their treatment regimen to their level of severity was employed.
Outcomes	Measurement of adherence: Three outcome measures directly assessed adherence to recommended regimens: a ten-item observational checklist to assess inhaler use skills, self-report scales to determine adherence to medications and inhaler use, and subjective assessment on a three-point scale by a project staff member. Measurement of health care outcomes: Four status scales were employed in assessing health care outcomes: the first assessed the severity of asthma symptoms during the past seven days, the next focused on psychological/ psychosomatic aspects of asthma (whether the patients were 'bothered' by asthma in the past seven days), the next scale assessed the number of episodes of respiratory problems/diseases experienced in the last three months, and the final scale measured whether asthma had interfered with the patients' lives in the last three months (prevented them from doing something).
Notes	
Allocation concealment	B

Study	Baird 1984
Methods	Random allocation without indication of concealment.
Participants	Mild-moderate hypertensive patients who, at the time of study entry, were adequately controlled with a regimen of metoprolol 200 mg (range 150-250 mg) daily, or propranolol 160 mg (range 120-200 mg) daily, either as monotherapy or in conjunction with a diuretic were included in the study. Patients excluded from the study were those with a condition in which beta-blockade was contraindicated.
Interventions	Patients were taken off whatever beta-blocker they were taking at entry and then allocated to one of the 2 interventional groups: (1) Betaloc tablets 100 mg in the morning (0600-0900 hours), and in the evening (12 hours later), or (2) Betaloc Durules 200 mg every morning (0600-0900 hours).
Outcomes	Two measurements of adherence were utilised: (1) tablet counts at six and 10 weeks, and (2) spot checks of metoprolol concentration in the urine at six and 10 weeks. The mean heart rate, systolic and diastolic

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	blood pressures were assessed before, during, and after the trial, and compared between the two treatment regimens.
Notes	Outcome assessments not blinded to study group.
Allocation concealment	B

Study	**Becker 1986**
Methods	Random allocation without an indication of concealment.
Participants	Patients between the ages of 20 and 80 years who were already taking medication for previously diagnosed hypertension, and who had already demonstrated poor blood pressure control (diastolic blood pressure > 90 mm Hg) on at least one visit during the preceding two years were included in the study. Patients who had significant visual, auditory, or mental problems that could interfere with their adherence were excluded.
Interventions	Patients in the control group received all of their antihypertensive medications in the traditional pill vials (separate vials for each pill that were labelled with the drug name, the dosage, the medication instructions, and the physician's name), whereas patients assigned to the experimental group received all their medications in the special packaging format (all pills taken together were packaged in a single plastic blister sealed with a foil backing on which was printed the day of the week and the time of day at which each medication was to be taken). All medications for both groups were provided free of charge to ensure that all patients would receive their medications.
Outcomes	Patient self-reports of adherence, where patients were asked non-threatening, non-judgemental questions about their adherence behaviour (patients who admitted less than perfect adherence were considered non-adherent), and pill counts (patients were considered adherent if they had taken 80% or more of their prescribed medication) were employed in order to assess adherence. Blood pressure was taken three times during each visit. The first measure was discarded and an average of the second and third measures was used as the blood pressure measurement for that visit. Blood pressure control was defined as diastolic blood pressure less than 90 mm Hg.
Notes	All data collection was done by a nurse research assistant prior to regular office visits. Physicians caring for patients were aware that adherence studies were in progress, but were not told the aims of the study nor the group to which an individual patient had been assigned.
Allocation concealment	B

Study	**Brown 1997a**
Methods	The method of random allocation was not described.
Participants	Patients were men < or = 65 years of age at high risk for future cardiac events by virtue of: 1) an elevated apoprotein B > or = 125 mg/dl, 2) at least one coronary lesion > or = 50% stenosis or 2 lesions > or = 30% stenosis as documented by baseline angiogram, and 3) a family history of premature cardiovascular events.
Interventions	Regular niacin (qid) versus polygel controlled release niacin (bid). All patients received lovastatin 20 mg bid, colestipol 10 g bid, and niacin 500 mg qid for 12 months, with dosage adjustment to target cholesterol of 150 to 175 mg/dl, and to minimize side effects. At 12 months, patients were randomly assigned to 1) continue with regular niacin at a dose identical to that established during the 12 month dose-finding period, or 2) change to polygel controlled-release niacin at that daily dosage, but given twice rather than 4 times/day. At 20 months, groups 1) and 2) were reversed (crossover). This regimen continued for 8 more months.
Outcomes	Compliance with the recommended (and variable) dosage was calculated for each drug using a computer program that accounted for all drug supplies given, the recommended dosage, and a count of returned medication. It is expressed as a percentage of the dose recommended for the patient at the time. Clinical outcome measurements included plasma very low-density lipoprotein (VLDL), LDL, and HDL cholesterol, triglycerides, apolipoprotein B, and asparate aminotransferase measured at baseline and every 4 months. Other laboratory measurements included uric acid, fasting glucose, fasting insulin, creatinine kinase and fibrinogen at entry (before treatment), 6 months, 12 months, 20 months, 28 months, and 6 weeks after stopping the triple-drug regimen.

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Characteristics of included studies (*Continued*)

Notes	
Allocation concealment	B

Study	**Brus 1998**
Methods	Patients were allocated at random to experimental (n=29) or control group (n=31). The randomisation was carried out blockwise per rheumatologist. No statement concerning concealment of allocation. Outcome assessors were blinded for allocation.
Participants	Patients suffering from RA (ACR Criteria) for less than three years. Active disease defined by an erythrocyte sedimentation rate (ESR) greater than 28 mm 1st hour, the presence of six or more painful joints, and the presence of three or more swollen joints. DMARD therapy with sulphasalazine had to be indicated by the attending rheumatologist and agreed for by the patients. Patients who had used any DMARD other than hydroxychloroquine were excluded.
Interventions	The experimental group attended six patient education meetings. The education programme focused on compliance with sulphasalazine therapy, physical exercises, endurance activities (walking, swimming, bicycling), advice on energy conservation, and joint protection. Four (two hour) meetings were offered during the first months. Reinforcement meetings were given after four and eight months. The programme was implemented in groups and partners were invited to attend the meetings. One instructor (HB) provided information on RA, attendant problems, and basic treatment. The related beliefs of the patients were discussed and, when necessary, corrected. If patients anticipated problems with the applications of any of the treatments, these were discussed, including possible solutions. A training was given in proper execution of physical exercise. Patients were encouraged to plan their treatment regimens. Their intentions were discussed and help was given in recasting unrealistic ones. Patients made contracts with themselves regarding their intentions. Feedback on the eventual implementaion fo therapeutic advice was included in each meeting. The control group received a brochure on RA, as provided by the Dutch League against Rheumatism. This brochure gives comprehensive information on medication, physical and occupational therapy. Sulfasalazine in the form of 500mg enteric coated tablets was prescribed to all patients. The daily dose was increased in four weeks by steps of one tablet, until a daily dose of four tablets was reached. In individual cases, this could be increased to six tablets a day, reduced as deemed necessary, or stopped in case of inefficacy or toxicity, at the description of the attending rheumatologust. All patients obtained the sulphasalazine tablets from the pharmacists according to the local Health Care System.
Outcomes	Compliance with sulfasalazine therapy was evaluated at 3, 6, and 12 months. Medical records and pharmacy records were the source of data on the number of tablets prescribed and the number of tablets obtained. At each evaluation, the number of remaining tablets were counted. Compliance was defined as the number of tablets that had been taken during the preceding period divided by the number of tablets prescribed Disease activity was measured by the disease activity score (DAS). This is a function of ESR, Ritchie score (0-78) and number of swollen joints (0-52). The DAS ranges from 0-10, where o represents the lowest level of disease activity possible, and 10 the highest. Physical funtions was measured by a Dutch version of the M-HAQ. The Dutch-AIMS questionnaire was used to assess physical function, psychological function, pain and social activities. Compliance rates with prescriptions for physical exercise and with endurance activity regiments (walking, swimming, bicycling) were measured by questionnaire. Compliance with prescriptions for energy conservation was measured by questioning whether patients spread their activities over the day to prevent fatigue. A test for joint protection performance was used as an indication for the level of compliance with the prescription of joint protection. Patients were asked to perform actions, representing relevant ergonomic principles. The test score ranges from 0 to 10, where 0 represents a poor performance and a 10 good performance.
Notes	
Allocation concealment	B

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Characteristics of included studies (*Continued*)

Study	**Chaplin 1998**
Methods	Patients were randomly assigned to 2 groups of 28 patients each. No statement concerning concealment of randomization.
Participants	Patients were included if they had an ICD-10 diagnosis of functional psychosis, were clinically stable, living in the community, and receiving anti-psychotic medication for at least 6 months. Patients were excluded if they were prescribed clozipine or were hospital in-patients. Sixty patients were approached. Fifty-six patients agreed to participate.
Interventions	The study group participated in a discussion about the risks and benefits of neuroleptic medications based on individual semi-structured educational sessions with reference to a standardised information sheet modified from Kleinman et al (1989). The patients were asked whether they had heard of tardive dyskinesia. The common movements of TD were modelled and the patients were asked whether they thought they had the condition or had seen others with it. They were informed that they were receiving an antipsychotic drug and were given information about extrapyramidal symptoms and TD, its risk factors, prevalence, treatment, potential irreversibility and the 1% risk of TD in non-antipsychotic-treated patients. They were told that gradual discontinuation of antipsychotic medication was the best way to prevent the condition but if done abruptly carries a high risk of relapse and of precipitating TD. It was stated that the optimum maintenance treatment, taking into account its risks and benefits, was to use the lowest dose of antipsychotic drug that would keep them well. Most importantly, they were asked not to make any changes to their treatment without discussion with their psychiatrist. Finally, they were given the opportunity to ask questions in an informal interactive session lasting 30 minutes, and were given an information sheet for reference. The control group received usual care.
Outcomes	1. Relapse, defined as a period of hospitalization, evidence of clear clinical deterioration in the case-notes or in discussion with the keyworker, or evidence of deterioration at follow-up interview. 2. Increase in antipsychotic dose of >200 mg chlorpromazine equivalents. 3. If the patient missed more than 2 weeks of their antipsychotic meds they were considered non-compliant.
Notes	In this study, th intent was not to increase compliance; rather it tested whether information about benefits and adverse effects of the treatment would decrease compliance.
Allocation concealment	B

Study	**Colcher 1972**
Methods	Random allocation without an indication of concealment.
Participants	All children (aged 1-15) presenting to a pediatric outpatient clinic with streptococcal pharyngitis were included except those known to have received previous antimicrobial therapy of any type during the previous month, or those known to be allergic to penicillin.
Interventions	The parents of the 'normally informed' group were given instructions that the penicillin was to be taken three times per day for ten days, and any questions that they had were answered. Parents of the 'optimally informed' group received specific counselling stressing the necessity that the penicillin be taken for the full ten days in order to achieve the best cure/prevent relapse, and further, were given written instructions.
Outcomes	There was a single measurement of adherence: Sarcina lutea growth inhibition by urine (a test for the presence of antimicrobial activity). Throat cultures were obtained at nine days, three and six weeks post-treatment. As well, the incidence of relapse was estimated in the various patient groups.
Notes	No indication of blinding of outcome measures.
Allocation concealment	B

Study	**Cote 1997**
Methods	The method of random allocation was not described.
Participants	Patients were 16 years of age or older, with moderate to severe asthma and the need to take daily anti-inflammatory agent. The diagnosis of asthma was confirmed by either a documented reversibility greater

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	than 15% in FEV1 or a PC20 methacholine less than or equal to 8 mg/ml when determined by the method described by Cockcroft and coworkers.
Interventions	The intervention is an asthma education program with an action plan based on peak-flow monitoring (Group P) or an action plan based on asthma symptoms (Group S). The Control group (Group C) received instructions from their pulmonologists regarding medication use and influence of allergenic and nonallergenic triggers. They were taught how to use their inhaler properly by the educator. A verbal action plan could be given by the physician. Groups P and S received the same education as the Controls plus individual counselling with the specialized educator during a 1-hour session. All participants received a book entitled "Understand and Control Your Asthma" at no extra charge. Group P received a self-management plan based on peak expiratory flow (PEF). They were asked to continue measuring PEF twice a day and to keep a diary of the results. Each time, subjects only recorded the best of three measurements. Every attempt was made to ensure that patients knew how to interpret the measurement and how to respond to a change in PEF. At each follow-up visit, the patient's diary card was reviewed, and if the action plan had not been implemented when required, further explanations were given regarding when treatment should be modified. Group S received a self-management plan based on asthma symptom monitoring. These patients were asked to keep a daily diary of asthma symptom scores, using a scale of 0 (no symptoms) to 3 (nighttime asthma symptoms, severe daily symptoms preventing usual activities), and adjust their medications according to the severity of respiratory symptoms using the guidelines of the action plan.
Outcomes	Adherence was assessed at each follow-up by weighing the used medication canisters. Patients were unaware of this. Treatment outcome was assessed, in terms of asthma morbidity, by a count of the days missed from work or school, the number of hospitalizations or visits to the emergency room for asthma, and the number of oral corticosteroids courses used since their last visit. These were self-reported in a diary and recorded at each of the 1, 3, 6, 9, and 12 month visits after randomization. Data regarding the number of visits to the emergency room, number of hospitalizations, and absenteeism at work or school during the 12 months prior to enrollment in the study were also collected for all patients by administering a questionnaire and reviewing the medical charts. Knowledge of asthma was also measured pre-run-in, at randomization and at the final visit using a questionnaire.
Notes	To reduce financial barriers to treatment adherence, the investigators supplied asthma medication at no charge throughout the trial.
Allocation concealment	B

Study	**Friedman 1996**
Methods	Random allocation using a paired randomization protocol.
Participants	Patients were 60 years or older, under the care of a physician for hypertension and prescribed an antihypertensive medication. They needed to have systolic blood pressure greater than or equal to 160 mmHg or a diastolic blood pressure greater than or equal to 90 mmHg based on an average of two determinations taken 5 minutes apart. Individuals were excluded if they had a life-threatening illness, were not English-speaking, did not have a telephone or could not use one, or refused to consent to participate.
Interventions	Control patients received regular medical care. The intervention group received regular medical care plus the telephone-linked computer system (TLC). TLC is an interactive computer-based telecommunications system that converses with patients in their homes, using computer-controlled speech, between office visits to their physicians. The intervention patients would call the TLC on a weekly basis. Before calling, subjects would record their own blood pressure using an automated sphygmomanometer with a digital readout. During the conversation, subjects would answer a standard series of questions and the TLC would provide education and motivational counselling to improve medication adherence. The TLC then transmitted the reported information to the subject's physician.
Outcomes	Antihypertensive medication adherence was assessed by home pill count conducted by the field technicians. Clinical outcome measures included change in systolic and diastolic blood pressure. Outcome measures were

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	recorded by the field technicians, at the two home visits performed 6 months apart. The measures were also reported on a weekly basis by the participant.
Notes	
Allocation concealment	B

Study	**Gallefoss 1999a**
Methods	This paper describes the same patients as Gallefoss & Bakke, 1999. Random allocation. Concealment of allocation unclear. Outcome assessors were blinded to allocation group.
Participants	Eligible subjects were patients with bronchial asthma and COPD between 18 and 70yr of age, not suffering from any serious disease such as unstable coronary heart disease, heart failure, serious hypertension, diabetes mellitus, kidney or liver failure. Subjects with asthma were to have a FEV1 equal to or higher than 80% of predicted value in stable phase. Furthermore a positive reversibility test, a documented 20% spontaneous variability (PEF and FEV), or a positive metacholine test were required.
Interventions	The intervention group received a specially made 19-page booklet with essential information about asthma/COPD, medication , compliance, self-care, and self-management plan. Instructions in the recoding of PEF and symptoms in a diary were given to both asthmatics and patients with COPD. The asthmatics and patients with COPD were educated in separate groups. The COPD group received more information about tobacco weaning, but besides this the educational interventions were comparable. The education consisted of two 2-h group sessions of five to eight persons on two separate days. The subjects then had one to two individual sessions by a nurse and one to two individual sessions by a physiotherapist.
Outcomes	4 simple HRQoL questions were asked at baseline. HRQoL as measured by the St-George's Respiratory Questionnaire (SGRQ) at 12 mos plus the same 4 questions asked at baseline. FEV measured via spirometry prior to randomization and at 12 mos.
Notes	Same study as Gallefosse and Bakke 1979.
Allocation concealment	B

Study	**Gallefoss 1999b**
Methods	At inclusion, patients signed a written consent and were then randomized to an intervention group or a control group. Concealment of allocation was unclear. Technical staff assessing bronchodilator spirometry were blinded for control and intervention patients.
Participants	Eligible subjects were patients with bronchial asthma or COPD between 18 and 70 yrs. of age, not suffering from any serious disease, such as unstable coronary heart disease, heart failure, serious hypertension, diabetes mellitus, kidney or liver failure. Participants with stable asthma were to have a prebronchodilator FEV1 equal to or higher than 80% of predicted value "in stable phase". Furthermore, either a positive reversibility test, a documented 20% spontaneous variability (PEF or FEV1) or a positive methacholine test (provocative dose causing a 20% decrease in FEV1 [PD20] was required. A positive reversibility test required at least a 20% increase (FEV1 or PEF) after inhalation of 400ug salbutamol. Subjects with COPD were to have a prebronchodilator FEV1 equal to or higher than 40% and lower than 80% of predicted.
Interventions	The control group were followed by their GPs and the intervention group received an education program and were then also transferred to a 1-yr. follow-up by their GPs. The educational intervention consisted of a specially constructed patient brochure, two 2-hour group sessions (separate groups for asthmatics and patients with COPD). The first session was given by a medical doctor, concentrating on pathophysiology, symptom awareness, prevention of attacks and factors causing exacerbations, especially smoking. The second group session was given by a pharmacist, focusing on drugs and their appropriate use. One or two 40-min individual sessions were then supplied by a nurse and another one or two 40-minute sessions, by a physiotherapist. With regard to antiobstructive medication the following was emphasized: the components of obstruction were explained together with the site of action of the actual

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	medication. The patient's pulmonary symptoms were registered and discussed with emphasis on the early symptoms experienced at exacerbations. The individual factors causing attacks/exacerbations and concerns regarding adverse effects of medication were discussed and inhalation technique was checked. At the final teaching the patients received an individual treatment plan on the basis of the acquired personal information and 2 wk of peak flow monitoring. The personal understanding of the treatment plan with regard to changes in PEF and symptoms was discussed and tested
Outcomes	Compliance of regular medication was calculated as a %age: (dispensed Defined Daily Dosage/ Prescribed Defined Daily Dosage)x 100 during the 1-yr. follow-up. Patients were defined as compliant when dispensed regular medication was greater than 75% of prescribed regular medication during the study period. Prebronchodilator spirometry was performed before randomization and at 12 month follow-up by standard methods.
Notes	Patients who failed to attend all group sessions or who failed to meet at individual sessions were withdrawn. There was no similar "faintness of heart" procedure for the control group. Thus, 38 of 39 control asthma patients were included in the compliance assessment but only 30 of 39 intervention group patients. (2p=0.014 by Fisher's exact test)
Allocation concealment	B

Study	**Girvin 1999**
Methods	Randomization was conducted by an independent advisor by resampling without replacement after the placebo run-in period. The study was not double-blind because one outcome was the difference in compliance between once-daily and twice-daily regimens. However, the investigator responsible for analyzing the results was blinded as to the treatment phase.
Participants	27 Patients with a history of mild hypertension (well controlled on monotherapy), with a diastolic bp between 90-110 mmHg were included. Patients were excluded if they had secondary hypertension or significant end organ damage, were pregnant or lactating mothers, had cardiovascular complications in addition to hypertension (e.g. MI within the past 6 months), stroke, congestive heart failure, angina pectoris, had poor renal function, a history of renal artery stenosis, were obese (weighing over 125% of ideal body weight) had hyperkalemia, had a history of angioneurotic oedema, had any contraindication or hypersensitivity to ACE inhibitors, or if they were taking NSAIDS, corticosteroids or any other medication that would significantly alter blood pressure
Interventions	Patients were randomly assigned to a sequence of enalapril 20mg once daily or 10mg twice daily in three 4-week periods following a 4-week run-in period. Treatment A comprised enalapril 20mg once daily, and treatment B comprised enalapril 10 mg twice daily. The first two periods in each group constituted a conventional 2-period crossover design. The third treatment period was included to detect any carryover effects between the periods without having to incorporate a washout phase between treatments. The 4 study arms were organized as follows (each period lasted 4 weeks): ABB BAA ABA BAB
Outcomes	Measurement of Compliance: Patient compliance was measured via pill counts and electronic monitoring using MEMS, which record the exact date and time of each opening and closing of the drug container. Measurement of Clinical Health Outcomes: Blood pressure reduction was measured at each visit. Patients were asked not to take their blood pressure tablet on the morning of the clinical visit until after the investigator had measured their blood pressure so that the BP readings were trough values. Two readings were taken after 10 min rest in the seated position. The arm was supported at heart level and the diastolic blood pressure taken as the disappearance of the Korotkoff sounds (phase V). Ambulatory blood pressure was measured at the end of the placebo run-in period and at the end of periods 1 and 2.
Notes	

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Allocation concealment	B

Study	**Haynes 1976**
Methods	Random allocation by 'minimisation', a method stated to be impervious to bias.
Participants	This was the second phase of a two phase study. Male steel company employees with high blood pressure (when sitting quietly on three separate days, a standard series of fifth phase diastolic blood-pressures were >95 mm Hg) who were treated with antihypertensive medications during the first phase of the study were included in the second phase if they were nonadherent with prescribed antihypertensive therapy (pill counts less than 80%), and not at goal blood pressures (fifth phase < 90 mm Hg) in the sixth month of treatment of phase 1.
Interventions	Patients in the experimental group were all taught the correct method to measure their own blood pressures, were asked to chart their home blood pressures and pill taking, and taught how to tailor pill taking to their daily habits and rituals. These men also visited fortnightly at the worksite a high-school graduate with no formal health professional training who reinforced the experimental manoeuvres and rewarded improvements in adherence and blood pressure. Rewards included allowing participants to earn credit, for improvements in adherence and blood pressure, that could be applied towards the eventual purchase of the blood pressure apparatus they had been loaned for the trial. Control patients received none of these interventions.
Outcomes	An unobtrusive pill count done in the patient's home by a home visitor was the method of determining medication adherence. Adherence rates are reported as the proportion of pills prescribed for the twelfth month of therapy which were removed from their containers and, presumably, swallowed by the patients. In the twelfth month of treatment, patients were evaluated for adherence and blood pressure both at home and at the mill by examiners who were 'blind' to their experimental group allocation.
Notes	
Allocation concealment	A

Study	**Henry 1999**
Methods	119 patients were randomly allocated to intervention (n=60) and control (n=59) groups. The trial was single blinded in that, although patients were aware of the names of the study medication and the fact the study was an H. Pylori treatment trial, they were unaware of either the differences between the treatment groups or the compliance enhancing purpose of the trial.
Participants	All adult patients over the age of 18 years with H. Pylori infection were screened for eligibility. Patient exclusion criteria included inability or refusal to give informed consent, contraindication to the study medication, consultant's recommendation not to treat patient, consultant wish to use an H. pylori therapy other than the study medication, and inpatient status as patient compliance is imposed in this situation.
Interventions	ALL patients received 10 days of omeprazole 20 mg b.d., amoxycillin 500 mg t.d.s., and metronidazole 400 mg t.d.s., as well as verbal advice on medication use and possible side effects, in an initial 20 minute consultation. In addition, patients in the intervention group received medication in dose-dispensing units, an information sheet on H. Pylori treatment, and a medication chart. Compliance in intervention group patients was also encouraged by a phone call 2 days after the start of therapy.
Outcomes	Measurement of compliance: Compliance was assessed by phone interview on day 10 of therapy, and by returned tablet count at the follow-up C-urea breath test (C-UBT) visit. Patients were defined as compliant if they were assessed by both pill count and interview as taking =80% of study medications. Total percentage of tablets taken in both groups was assessed by taking the lower of the two estimates of tablet consumption (pill count or interview data) for each patient. Measurement for health care outcomes: Patients were considered H. Pylori- positive if the CLO-test, histopathology, or 13C-UBT was positive. 13C-UBT test using kits sent to a single central laboratory for analysis was performed for more than one month after cessation of H. pylori treatment and any other antimicrobial therapy (including bismuth), 2 weeks after cessation of proton-pump inhibitor therapy and 1 week after cessation of histamine-receptor antagonists.

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	An increase of 5 per million in the CO2 30 min after ingestion of C-urea compared with baseline measurements was considered positive for H. Pylori. Treatment was considered successful if 13C-UBT was negative. Side effects were assessed by phone interview on day 10 of therapy and by returned side effects form. Patients were asked to rate specific side effects and give an overall rating where none = 0, mild = 1 (does not limit daily activities), moderate = 2 (interferes with daily activities), and severe = 3 (incapacitating, stops normal daily activities).
Notes	
Allocation concealment	B

Study	**Howland 1990**
Methods	Method of randomisation not stated. The physician educating the patients was not blinded, whereas the office nurse questioning patients in the follow-up period was blinded as to which patient was in which group.
Participants	All patients over 18 years treated with erythromycin for an acute illness were included, while patients with a history of allergy/intolerance to erythromycin were excluded.
Interventions	Informed patients were told of six possible side-effects of treatment with erythromycin, while control (uninformed) patients were not made aware of potential side effects of treatment.
Outcomes	The occurrence of side effects both before and after treatment.
Notes	Adherence measured as the mean number of erythromycin pills taken per day, patients reporting that they missed at least one pill, and mean number of pills taken out of 40 pills.
Allocation concealment	B

Study	**Johnson 1978**
Methods	Random allocation in a 2x2 factorial design. No statement concerning concealment of randomisation.
Participants	Volunteers from shopping centre blood pressure screening in Canada, with follow-up by usual family doctors. Men and women aged 35-65 who had been receiving antihypertensive medications for at least one year, but whose diastolic blood pressure had remained elevated.
Interventions	The interventions consisted of (1) self-recording and monthly home visits, (2) self recording only, (3) monthly home visits, and the control group consisted of (4) neither self-recording nor home visits. Subjects in groups (1) and (2) received a blood pressure kit and instruction in self-recording. Patients in the self-recording groups were to keep charts of their daily blood pressure readings and were instructed to bring these charts to their physician at each appointment. Subjects in groups (1) and (3) had their blood pressure measured in their homes every four weeks, and the results were reported to both the patient and the physician.
Outcomes	Adherence with therapy was assessed by interview and pill counts (the percentage of prescribed pills that had been consumed was estimated by comparing pills on hand at a home visit with prescription records of pills dispensed and the regimen prescribed). Changes in mean diastolic blood pressure (mm Hg) were assessed. Since the initial blood pressure bears an important relation to the change in blood pressure over time, the change scores were adjusted for differences in entry values by covariance analysis. Outcome assessors were blinded to study group.
Notes	
Allocation concealment	B

Study	**Katon 2001**
Methods	Patients were randomized to the relapse prevention intervention vs. usual care in blocks of 8. Within each block, the randomization sequence was computer-generated. The telephone survey team conducting the follow-up assessments (at 3,6,9 and 12 months) were blinded to randomization status. Patients could not be blinded due to the nature of the intervention (i.e. patient education, visits with depression specialist, telephone monitoring and follow-up). The primary care physicians were also not blinded.

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Characteristics of included studies (*Continued*)

Participants	Patients between the ages of 18 and 80 years who received a new antidepressant prescription (no prior prescriptions within the previous 120 days) from a primary care physician for the diagnosis of depression or anxiety were eligible for the study. Inclusion criteria for the relapse prevention study obtained during the baseline interview included patients with fewer than 4 DSM-IV major depressive symptoms and a history or 3 or more episodes of major depression or dysthymia or 4 residual depressive symptoms but with a mean SCL-20 depression score of less than 1.0 and a history a major depression/dysthymia. Exclusion criteria included having a screening score of 2 or more on the CAGE alcohol screening questionnaire, pregnancy or currently nursing, planning to disenroll from GHC within the next 12 months, currently seeing a psychiatrist, limited command of English, or recently using lithium or antipsychotic medication.
Interventions	The intervention included patient education, 2 visits with a depression specialist, and telephone monitoring and follow-up. Before the first study visit, the intervention patients were provided a book and videotape developed by the study team that was aimed at increasing patient education and enhancing self-treatment of their depression. They were also scheduled for 2 visits with a depression specialist (one 90-minute initial session and one 60-minute follow-up session) in the primary care clinic. Three addition telephone visits at 1, 4, and 8.5 months from session 2 with the depression specialist and 4 personalized mailings (2,6,10 and 12 months) were scheduled over the following year. The mailed personalized feedback contained a graph of patients' Beck Depression scores over the course of the intervention program and checklists for patients to send back to the depression specialist, including early warning signs of depression and whether they were still adhering to their medication plan. The depression specialist reviewed monthly automated pharmacy data on antidepressant refills and alerted the primary care physician and telephoned the patients when mailed feedback or automated data indicated they were symptomatic and/or had discontinued medication. The ultimate aim of the intervention was to have each patient complete and follow a 2-page written personal relapse prevention plan, which was also shared with his/her primary care provider. Follow-up telephone calls and mailings were geared toward monitoring progress and adherence to each patient's plan. Usual care for most patients was provided by the GHC family physicians in the 4 primary care clinics and involved prescription of an antidepressant medication, 2 to 4 visits over the first 6 months of treatment, and an option to refer to GHC mental health services. Both intervention and control patients could also self-refer to a GHC mental health provider
Outcomes	Measurement of Compliance: Patients' adherence to antidepressant medication was measured at 3,6,9 and 12 months after randomization by a telephone interviewer. Based on computerized automated data from prescription refills, patients were rated as adherent at the 3-, 6-, 9- and 12-month follow-up periods as well as whether they received adequate dosage of antidepressant medication for 90 days or more during the 1-year period. The lowest dosages in the ranges recommended in the Agency for health Care Policy and Research guidelines developed for newer agents were used to define a minimum dosage standard. Measurement of Clinical Health Outcomes: Baseline and follow-up interviews assessing depressive symptoms (at 3-, 6-, 9- and 12-months) included the SCL-20 depression items (scored on a 0-4 scale), the dysthymia and current depression modules of the SCID, the NEO Personality Inventory Neuroticism Scale and the Longitudinal Interval Follow-up Evaluation to measure incidence and duration of episodes within each 3-month block of time.
Notes	
Allocation concealment	B

Study	**Kemp 1996**
Methods	Random allocation by means of a table of random numbers.
Participants	Patients between the ages of 18 and 65 who were admitted to hospital with acute psychosis over eight months. DSM III-R diagnoses of subjects included schizophrenia, severe affective disorders, schizophreniform, schizoaffective disorder, delusional disorders, and psychotic disorder not otherwise classified. Non-English speakers and subjects with low IQ scores, deafness, or organic brain disease were excluded.
Interventions	Control group treatment consisted of 4 to 6 supportive counselling sessions with the same therapist. Therapists listened to patient concerns but declined to discuss treatment.

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	Experimental intervention treatment consisted of 4 to 6 sessions of "compliance therapy" - a strategy that borrows from motivational interviewing. During session 1 and session 2, patients reviewed their illness and conceptualised the problem. In the next 2 sessions, patients focused on symptoms and the side effects of treatment. In the last 2 sessions, the stigma of drug treatment was addressed.
Outcomes	Adherence scores were measured using a 7-point scale (1 = complete refusal to 7= active participation and ready acceptance). Measures were obtained preintervention, postintervention, at 3 month follow-up and at 6 month follow-up. Outcome measures included ratings on a brief psychiatric rating scale, global functioning assessment, and dose of antipsychotic drug.
Notes	
Allocation concealment	A

Study	**Kemp 1998**
Methods	Random allocation by means of a table of random numbers.
Participants	Patients between the ages of 18 and 65 who were admitted to hospital with acute psychosis over 14 months. DSM III-R diagnoses of subjects included schizophrenia, severe affective disorders, schizophreniform, schizoaffective disorder, delusional disorders, and psychotic disorder not otherwise classified. Non-English speakers and subjects with low IQ scores, deafness, or organic brain disease were excluded.
Interventions	Control group treatment consisted of 4 to 6 supportive counselling sessions with the same therapist. Therapists listened to patients' concerns but when medication issues were broached, patients were directed to discuss such issues with their treatment teams. Experimental intervention treatment consisted of 4 to 6 sessions of "compliance therapy" - a strategy that borrows from motivational interviewing. During session 1 and session 2, patients reviewed their illness and conceptualised the problem. In the next 2 sessions, patients focused on symptoms and the side effects of treatment. In the last 2 sessions, the stigma of drug treatment was addressed.
Outcomes	Adherence scores were measured using a 7-point scale (1 = complete refusal to 7= active participation and ready acceptance of regimen). The clinical outcome measures included ratings on a brief psychiatric rating scale, global functioning assessment, schedule for assessment of insight, drug attitudes inventory, attitude to medication questionnaire, Simpson-Angus Scale for extrapyramidal side-effects. Measures were obtained in-hospital preintervention and postintervention. Following discharge, measurements were made at 3, 6, 12, and 18 months.
Notes	Initial compliance was rated by the patient's primary nurse. Follow-up compliance ratings were obtained using the seven-point scale, based on corroboration from as many sources as possible (mean number of sources was approximately 2).
Allocation concealment	A

Study	**Knobel 1999**
Methods	Patients were randomly allocated using a 2:1 (control:intervention) ratio. There are no details about the randomization procedure or whether it allowed for concealment of allocation. The study was not blinded.
Participants	There are no exclusion criteria. Inclusion criteria: all patients with HIV infection demonstrated by plasma viral load > 5000 copies/mL AND CD4+ lymphocyte count < 600 X 106/L initiating treatment with indinavir (800 mg q8h), zidovudine (300 mg q12h), and lamivudine (150 mg q12h). They included all patients with HIV infection receiving prescription for this combination of agents from 7/96 to 12/97.
Interventions	All patients were treated with zidovudine + lamivudine + indinavir. Control patients (n=110) received conventional care in addition to the drug regimen (new refill every 2 months). Intervention patients (n=60) received individualized counseling/assessments which consisted of adaptation of treatment to the patient's

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	lifestyle, detailed information about highly active antiretroviral therapy, phone support (for questions or medication-related problems), and monthly visits to the HIV day clinic.
Outcomes	Measurement of Compliance: Compliance was estimated every 2 months using a structured interview and by pill counts. The same person conducted all compliance evaluations blind to viral load (not to allocation). Patients were considered to be compliant when: (1) they took more than 90% of their drugs; AND (2) >90% of pill intakes should be according to a pre-specified schedule (hours between doses, relation between doses and meals); AND (3) less than 2 mistakes in pill intake per day. Clinical Health Outcomes: Undetectable viral load was measured, as was reduction in viral load and increase in CD4+ lymphocyte count.
Notes	
Allocation concealment	B

Study	**Levy 2000**
Methods	Patients were randomized consecutively into intervention and control groups using equal blocks of four generated using the Clinstat program. This was done by the two nurses at their respective hospitals, by first producing two patient lists, by date order of receipt of their consent forms i) completed when attending or ii) returned by post. 108 patients were randomly allocated into the control group, and 103 patients were randomly allocated into the intervention group. Study nurses were not blinded wrt allocation AFTER randomization occurred.
Participants	211 patients over 18 years old attending emergency room department for asthma were included. Exclusion criteria not specified, except that patients with a previously recorded diagnosis of COPD were excluded.
Interventions	The intervention group was invited to attend a 1h consultation with one of the nurses beginning 2 weeks after entry to the study, followed by two or more lasting half an hour, at 6-weekly intervals. The second and third could be substituted by a telephone call. Patients were phoned, by the nurse before each appointment in order to improve attendance rates. Patient's asthma control and management were assessed followed by education on recognition and self-treatment of episodes of asthma. The patients were taught to step-up medication when they recognized uncontrolled asthma using PEF or symptoms. The advice was in accordance with national guideline. Prescriptions were obtained from one of the doctors in the clinic or by providing the patient with a letter to their general practitioner. Patients presenting with severe asthma (severe symptoms of PEF below 60% of their best/normal)were referred immediately to the consultant. Patients in the control group continued with their usual medical treatment and were not offered any intervention during the study period.
Outcomes	Measurement of Compliance: The primary outcome was the patients' reported, appropriate adherence to self-management of mild attacks within the previous 2 weeks or severe attacks in the previous 6 weeks. Measurement for Clinical Health Outcomes: Home peak flow and symptom diaries. Patients recorded the best of 3 PEF readings in the morning and evening, and also recorded symptom scores daily for 7 days. QOL was also assessed using the SGRQ, and patients use of medical services was assessed.
Notes	
Allocation concealment	A

Study	**Logan 1979**
Methods	Stratified random allocation. No indication of concealment.
Participants	Employees with an average diastolic blood pressure from two screens of > 95 mm Hg or a diastolic blood pressure of 91-94 mm Hg and a systolic blood pressure > 140 mm Hg were considered eligible for the study if they met the following criteria: (1) no expected termination of employment in the year after entry into the study, (2) no treatment for at least three months before screening, (3) not taking other daily medication, oral contraceptives, or oestrogen replacement therapy, (4) not pregnant or planning to become so during the

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	year of the study, (5) no remediable form of secondary hypertension, and (6) no objections from their family physician.
Interventions	Participants of the regular care/control group saw their own physicians. Each physician received the guidelines for hypertensive evaluation and management, and the goal blood pressure that was to be sought by the nurse. Subjects in the work-site care group were attended by two experienced nurses who were taught to manage hypertension according to a standard protocol. The nurses dealt with all aspects of hypertensive management but difficult problems were referred to the supervising physician, and unrelated medical problems were referred to the family physician. The standard protocol was as follows: patients were given a diuretic (step 1) to which, if hypertension was not controlled on maximum diuretic dosage, propranolol or methyldopa was added (step 2). Occasionally a third drug, hydralazine or prazosin, was required (step 3).
Outcomes	A questionnaire was administered to determine adherence with therapy. Participants who stated that they were taking their tablets were visited at home to assess exact adherence by an unobtrusive pill count (adherence was determined by noting the date, type and number of pills dispensed for the most recent prescriptions, assuming that missing pills represented consumption). Medication adherence was judged to be high if the patient claimed to be taking medications as instructed and if 80% or more of the prescribed drug was consumed, as determined by pill counts. At the six month evaluation, three blood pressure readings were taken. Goal blood pressure was defined as a reduction in diastolic blood pressure to less than 90 mm Hg in those with an entry diastolic blood pressure greater than 95 mm Hg, or a reduction in diastolic blood pressure of at least 6 mm Hg in those with an entry diastolic blood pressure of 95 mm Hg or less. Outcome assessors were blinded to study group.
Notes	
Allocation concealment	B

Study	**Logan 1981**
Methods	Cost-effectiveness analysis, based on original data, for Logan et al, 1979.
Participants	
Interventions	
Outcomes	
Notes	See Logan et al 1979.
Allocation concealment	B

Study	**Merinder 1999**
Methods	Patients were block-randomized, stratified for gender and for illness duration. The randomization was carried out by an independent institution. Due to the nature of the intervention, patients could not be blinded. Ratings of psychopathology and psychosocial function were performed by researchers who were not informed of treatment allocation. Relapse and compliance outcomes were assessed by researchers blind to the allocation of the patients.
Participants	Patients aged 18-49 years and a clinical ICD-10 diagnosis of schizophrenia and in treatment at the time of recruitment were included. Patients were included based on a clinical diagnosis, validated by the use of OPCRIT (operational criteria checklist for psychotic and affective illness) on case records.
Interventions	The control group received usual treatment provided in community psychiatry. The experimental group received an 8-session intervention using a mainly didactic interactive method. The programme was standardized with a manual for group leaders, overhead presentations and a booklet for participants. Patient and relative interventions were conducted separately, with group sizes in both patient and relative groups of 5 to 8 participants. The programme was the same for both patients and relatives, and sessions were conducted weekly

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Characteristics of included studies (*Continued*)

Outcomes	Compliance Measurements: Compliance measures were made at baseline and at follow-up (12 months after start of intervention). A non-compliance episode was rated if the case notes indicated that the patient did not receive medication for a period of 14 days. Measurement of Clinical Health Outcomes: Patient outcome measures included knowledge, relapse, psychosocial function, insight and satisfaction. The following scales were used: OPCRIT - operational criteria checklist for psychotic illness BPRS- brief psychiatric rating scale GAF - global assessment of function IS - insight scale VSS - Vern service satisfaction scale Also, knowledge of schizophrenia was evaluated
Notes	
Allocation concealment	B

Study	**Peterson 1984**
Methods	Coin toss randomisation.
Participants	Adult and teenage epileptic patients who were consecutive attenders at outpatient clinics during a four month period, who were responsible for their own medication, and who possessed a hospital pharmacy prescription book were included in the study.
Interventions	Patients in the intervention group received several adherence-improving strategies: patients were counselled on the goals of anticonvulsant therapy and the importance of good adherence in achieving these goals, a schedule of medication taking was devised that corresponded with the patient's everyday habits, patients were given a copy of an educational leaflet, each patient was provided with a 'Dosett' medication container and counselled on its utility, patients were instructed to use a medication/seizure diary, and patients were reminded by mail of upcoming appointments and of missed prescription refills. The control group received none of these interventions. The mean daily dosages of the most commonly prescribed anticonvulsant drugs (phenytoin, carbamazepine, and sodium valproate) were not significantly different between the two groups.
Outcomes	Each patient had plasma anticonvulsant levels measured (provided that the patient's medication regimen had not been altered in the preceding two weeks), the patient's prescription record book was checked to assess prescription refill frequency (if the refill frequency was one or more weeks later than expected at least once during the previous six months, the patient was considered non-adherent), and patient appointment keeping frequency (patients who had attended all their scheduled appointments in the previous six months were considered compliant) were assessed. The median number of self-recorded seizures experienced by each patient was compared between the control and intervention groups.
Notes	Physicians were blinded to the intervention group of their patients.
Allocation concealment	B

Study	**Peveler 1999**
Methods	Immediately after referral patients were individually randomized in blocks of 8 to one of four treatment groups by prearranged random number sequence, stratified by drug type, in a factorial design. Patients were unaware of their allocation at first interview and were asked not to reveal drug-counseling sessions to the interviewer subsequently.
Participants	Patients were included if they were aged 18 or over and starting new courses of treatment with dothiepin or amitriptyline. Inclusion was based on clinical diagnosis of depressive illness. Patients were excluded if they had received either drug within 3 months, had a contraindication (allergy, heart disease, glaucoma, or pregnancy) or were receiving other incompatible drugs. Any patients at high risk of suicide were also excluded.
Interventions	The four treatment groups were as follows: treatment as usual, leaflet, drug counseling, or both interventions. The information leaflet contained information about the drug, unwanted side effects, and what to do in

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	the event of a missing dose. Patients were given drug counseling by a nurse at weeks 2 and 8, according to a written protocol. Sessions included assessment of daily routine and lifestyle, attitudes to treatment, and understanding of the reasons for treatment. Education was given about depressive illness and related problems, self-help and local resources. The importance of drug treatment was emphasized, and side effects and their management discussed. Advice was given about the use of reminders and cues, the need to continue treatment for up to 6 months, and what to do in the event of forgetting a dose, and the feasibility of involving family or friends with medicine taking was explored.
Outcomes	Measurement of Compliance: At 6 weeks, self-reported adherence was assessed and was reassessed at the final visit. To check the reliability of self-reported adherence, adherence was measured in a subgroup using a MEMS monitor. Patients were seen at 3 weeks to resupply drugs and pills were counted. At 6 weeks the container was collected and the cap data was downloaded. Measurement of Clinical Health Outcomes: Depressive symptoms were measured by the hospital anxiety and depression scale and functional status was measured by the SF-36 health survey. Interviews were conducted at baseline, 6 weeks, and when drugs were discontinued at 12 weeks (whichever was sooner). Also, at 6 weeks depressive symptoms and unwanted effects of treatment were assessed. At the final visit, satisfaction with treatment and unwanted effects were reassessed and the SF-36 repeated.
Notes	
Allocation concealment	A

Study	**Piette 2000**
Methods	Of the 588 patients identified as potentially eligible, 280 patients were enrolled and randomized to a treatment arm, 137 to intervention, 143 to control. Randomization was based on a table of randomly permuted numbers. Patients, care givers, and outcome assessors were not blinded to patient allocation.
Participants	Patients included had a diagnosis of diabetes mellitus or an active prescription for a hypoglycemic agent. Patients were excluded if they were > 75 years of age, had a diagnosed psychotic disorder, disabling sensory impairment, or life expectancy of <12 months, or whose primary language was neither English nor Spanish. Patients were also excluded is they controlled their blood glucose levels without hypoglycemic medication, were newly diagnosed with diabetes (< 6 mos), planned to discontinue receiving services from the clinic within the 12-month follow-up period, or did not have a touch-tone telephone.
Interventions	The intervention consisted of a series of automated telephone assessments designed to identify patients with health and self-care problems (Teleminder Model IV automated telephone messaging computer). Calls were made on a biweekly basis, up to 6 attempted calls, and involved a 5 to 8-minute assessment. During each assessment, patients used the touch-tone keypad to report information about self-monitored blood glucose readings, self-care, perceived glycemic control, and symptoms of poor glycemic control, foot problems, chest pain, and breathing problems, with automated prompts for out-of-range errors. The automated telephone calls were also used to deliver, at the patient's option, 1 of 30 targeted and tailored self-care education messages at the end of each telephone session. Patients only received a 1-page instruction sheet on the use of the phone. Each week, the automated assessment system generated reports organized according to the urgency of the reported problems, and a diabetes nurse educator used these reports to prioritize contacts for a telephone follow-up. During follow-up calls, the nurse addressed problems reported during the assessments and provided more general self-care information. After several months, intervention group patients were offered additional automated self-care calls that focused on glucose self-monitoring, foot care and medication adherence. In the medication adherence part of these sessions, patients were asked about their adherence to insulin, oral hypoglycemic medications, antihypertensive medications, and antilipidemic medications. For each type of medication, patients without adherence problems received positive feedback and reinforcement. Patients reporting less than optimal adherence were asked about specific barriers and were given advice from the nurse about overcoming each barrier. The nurse was located outside the clinic and had no access to medical records other than the baseline info collected at enrollment and her own notes. She did not have any face-to-face contact with patients. The nurse addressed problems raised by patients in the automated calls and also gave general self-care education. The nurse also checked on patients who rarely responded to automated calls. A

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	small no. of patients initiated calls to the nurse by toll free no. She referred these to the primary care physician as appropriate. During the course of the trial, patients in the intervention groups averaged 1.4 automated calls per month and had 6 minutes of nurse contact per month. Patients assigned to the usual care control group had no systematic monitoring between clinic visits or reminders of upcoming clinic appointments. Providers used their discretion to schedule follow-up visits. Additional visits were scheduled at the patients initiative.
Outcomes	Measurement of Compliance: At baseline and 12 months, patients were surveyed by trained interviewers over the telephone. 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". Measurement of Health Care Outcomes: A 5-point Likert scale was used to measure self-care items such as glucose self-monitoring, foot inspection and weight monitoring. During interviews, patients reported whether they experienced each of 22 diabetes-related symptoms in the prior week (including symptoms of hyperglycemia, hypoglycemia, vascular problems, or other problems). Glycosylated hemoglobin and serum glucose levels were measured at baseline and a 12 months.
Notes	
Allocation concealment	A

Study	**Razali 2000**
Methods	The selected patients were randomly assigned to the study group (n=80), which received the CMFT, or control group (n=86), which received the BFT. Allocation was unblinded for treating psychiatrist and patient; outcome assessments were done by independent, blinded psychiatrists.
Participants	Recently discharged patients from the University Hospital with the diagnosis of schizophrenia (DSM-IV). Inclusion criteria included: at least 2 previous psychiatric admissions (including the latest admission), aged between 17-55 years, staying with a responsible relative who is willing to be involved in the study, stabilized for at least 4 weeks (stabilization was defined as rating of 4 or less on the BPRS psychotic items). Exclusion criteria not specified.
Interventions	The CMFT consists of a sociocultural approach of family education, drug intervention programme and problem-solving skills. The sociocultural approaches to family education include explanations of the concept of schizophrenia from a cultural perspective and an attempt to correct negative attitudes toward modern treatment. The family education and drug intervention was delivered as a package. The drug intervention programme includes drug counseling, [from Table 1] clear instruction about dose, frequency and possible side effects, the role of carers in supervision of medication at home, and close monitoring of compliance by a drug intake check-list presented in every follow-up visit. Both groups of patients received routine prescription of medication. It should be noted that the one psychiatrist treated the intervention group throughout the study, and a second psychiatrist treated the control group throughout the study. Patients in each group were followed-up on the same schedule; monthly for the first 3 months and then every 6 weeks in the next 9 months.
Outcomes	Measurement of Compliance: Measured at the end of 6 months and 1 year after initiation of the intervention. Medication compliance was assessed through a semi-structured interview with the carer and examination of the amount of unused medication. A home visit was made to assess unused medication "in doubtful cases". Drug compliance was measured globally as a percentage of the total prescribed drug dosage actually taken during the previous 6 months. The compliance was reported on a 6-point ordinal scale, with 1 indicating non-compliant, 2-25% compliant, 3-50% compliant, 4-75% compliant, 5-90% compliant and 6-100% compliant. 90% compliance was considered to be an ideal level. Measurement of Clinical Health Outcomes: Measured at the end of 6 months and 1 year after initiation of the intervention. Frequency of symptoms exacerbation, psychosocial functioning and behavioral difficulties were measured. Symptomatic exacerbation was determined by BPRS ratings. A rating of 5 or above in one or more of the psychoticism scales indicated an exacerbation. Overall psychosocial function was rated using

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	the Global Assessment of Function (GAF) of DSM-IV, while the Social Behavior Schedule (SBS) measured the behavioral difficulties.
Notes	
Allocation concealment	B

Study	**Sackett 1975**
Methods	Random allocation, 2x2 factorial design, no indication of concealment.
Participants	Male steel company employees who exhibited persistently elevated diastolic blood pressure on repeated examination (at or above 95 mm Hg (fifth phase)), were free of secondary forms of hypertension, were taking no daily medication, and had not been prescribed antihypertensive medications for at least six months before the trial were eligible for the study.
Interventions	Subjects in augmented convenience saw company physicians, rather than their family physicians, for hypertensive and follow-up care during paid working hours. The second intervention, mastery learning, was designed to give the facts about hypertension, its effects upon target organs, health, and life expectancy, the benefits of antihypertensive therapy, the need for adherence with medications and some simple reminders for taking pills (this information was provided in a slide-tape format, and reinforced by a secondary-school graduate 'patient educator').
Outcomes	Adherence was calculated by comparing the number of tablets prescribed with medications still on hand, by the semi-quantitative identification of drugs and metabolites in the urine, by the identification of characteristic changes in serum potassium and uric acid in men on thiazide drugs, and by patient self-report. Adherence is reported in terms of the percent of medication prescribed for the sixth month which was removed from the bottle and, presumably, consumed by the patient. Patients whose pill counts were consistent with adherence levels of 80% or more were considered 'compliant'. Blood pressure control was assessed by trained observers. Only patients whose diastolic blood pressure was below 90 mm Hg at six months would be designated as being 'at goal blood pressure'. Outcome assessors were blinded to study group.
Notes	
Allocation concealment	B

Study	**Strang 1981**
Methods	Random allocation, not otherwise specified.
Participants	Recently discharged patients with Present State Examination/CATEGO diagnoses of schizophrenia who were living with at least one parent who exhibited high 'expressed emotion' on the Camberwell Family Interview.
Interventions	All patients had scheduled therapy and monthly medication appointments. Patients were allocated to family therapy or individual support sessions. All patients received oral neuroleptic medication (usually chlorpromazine).
Outcomes	All patients were seen monthly by the prescribing psychiatrist, blinded to the group assignment, where medication status and adherence were assessed. Medication was adjusted based on mental status, side effects, and blood plasma levels. Patients with poor compliance for oral medications were given fluphenazine decanoate injections. Adherence was defined in six ways: number of missed appointments with psychiatrist; number of patients change to intramuscular depot medication; tablet-taking compliance (pill counts, self-reports by patient or family, and blood plasma levels); variability in plasma levels; mean and modal doses prescribed for each treatment group; mean plasma level in each group. Relapse was the treatment outcome (no information on how measured).
Notes	
Allocation concealment	B

Study	**Tuldra 2000**
Methods	116 patients were randomly allocated (no statement of allocation concealment) to one of two arms. 61 patients were randomized to the control group, and 55 were randomized to the "psychoeducative intervention" group.

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	There is no statement in the report about blinding of physicians. Patients and psychologists weren't blinded, and, if there was a separate outcome assessor, it isn't stated.
Participants	116 patients who initiated their first or second-line HAART at a general university hospital's HIV-outpatient unit were included. Exclusion criteria not specified.
Interventions	The experimental group received a psychoeducative assessment in addition to the regular clinical follow-up. The individual(s) who delivered the intervention is not identified, but is apparently, a psychologist, rather than the treating physician. The intervention was intended "primarily to improve patients' knowledge and customs in handling medication to increase self-efficacy". Patients in this arm received explanations about the reasons for starting treatment and the relevance of appropriate adherence to prevent replication of viral mutations and the development of antiretroviral drug resistance. Patients' doubts about medication intake were solved and a dosage schedule was developed with the patients' input. Study subjects were also taught to manage medication and tackle problems such as forgetting, delays, side effects and changes in the daily routine. A phone number was also given should any questions arise before the next interview. During follow-up visits, adherence was verbally reinforced and strategies were developed to deal with problems that had appeared to that point, including rescheduling dose schedules to overcome adherence problems, providing skills to deal with minor adverse effects. Patients in the control group received a standard assessment consisting of an interview with a psychologist following the regular medical visit, in which only variables related to adherence were recorded. The control group received only normal clinical follow-up. Both groups were interviewed for data collection at 0, 4, 24, and 48 weeks of follow-up.
Outcomes	Measurement of Compliance: Self-reported adherence was registered at each visit. The proportion of compliance was calculated by dividing the number of pills taken during the month before by the number of pills prescribed during the same period. Patients who consumed > 95% of medication prescribed were considered "adherent patients". Randomized blood analyses were also performed without warning in 40% of the patients to measure plasma levels of protease inhibitors (PI). Plasma levels of PI > 0.01mg/L indicated adequate compliance, PI levels <0.01 mg/dL indicated noncompliance. Measurement for Clinical Health Outcomes: HIV-1 RNA levels (copies/ml).
Notes	
Allocation concealment	B

Study	**Wysocki 2001**
Methods	At the end of baseline evaluation, a research assistant randomly assigned each family to one of the three groups. Randomization was stratified by the adolescent's sex and by the treatment center. (no statement of concealment of allocation). It is also unclear whether outcomes assessors were blinded. Due to the nature of the intervention, patients could not be blinded. It should be noted that despite randomization the three treatment groups differed demographically at baseline. The BFST group included significantly fewer intact families and more single-parents families than did the other two groups.
Participants	Inclusion criteria included the following: 12-17 years of age, having Type I diabetes > 1 year, no other major chronic diseases, no mental retardation, not incarcerated in foster care or in residential psychiatric treatment, no diagnoses of psychosis major depression or substance abuse disorder in adolescents or parents during the previous 6 months. Also, at least one family member had to obtain a score on the Diabetes Responsibility and Conflict scale > 24 or a score > 5 on the Conflict Behavior Questionnaire.
Interventions	Families were randomized to three months of treatment with either Behavioral-Family Systems Therapy (BFST), an education and support (ES) group, or current therapy (CT). Current Therapy - patients in the CT group (as well as those in the other groups) received standard diabetes therapy from pediatric endocrinologists, including an examination by a physician and a GHb assay at least quarterly; two or more daily injection of mixed intermediate- and short-acting insulins; self-monitoring of blood glucose and recording of test results; diabetes self-management training; a prescribed diet; physical exercise and an annual evaluation for diabetic complications.

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	Education and Support - In the first 3 months of the study, families attended 10 groups meetings that provided diabetes education and social support. A social worker at one center and a health educator at another center served as group facilitators. Panels of 2-5 families began and completed 10 sessions together; the parents and the adolescent with the diabetes attended the sessions. Family communication and conflict resolution skills were specifically excluded from session content, because these are the primary targets of BFST. Each session included a 45-min educational presentation by a diabetes professional, followed by a 45-min interaction among the families about a topic led by the facilitator. A monetary incentive, outlined below, was also provided to patients in this group. BFST- Adolescents and caregivers in this group received 10 sessions of BFST. BFST consisted of four therapy components that were used in accordance with each family's treatment needs as identified by the project psychologists and was based on study data and family interaction during sessions. The four therapy components included problem-solving training, communication skills training, cognitive restructuring and functional and structural family therapy. A monetary incentive, outlined below, was also provided to patients in this group. Monetary incentive - To maximize completion of data collection, families were paid $100 ($50 for parent, $50 for adolescent) on completion of each evaluation. ES and BFST families could earn another $100 if they completed all 10 scheduled intervention sessions.
Outcomes	Measurement of Compliance: A 14-item, validated Self-Care Inventory (SCI) was used to measure diabetes treatment adherence during the preceding 3 months. Higher scores indicate better treatment adherence. Questionnaires were given at baseline, at posttreatment (3 months) and at 6 and 12 months after treatment ended. Measurement of Clinical Health Outcomes: Glycated Hemoglobin (GHb) assays were conducted using affinity chromatography to index recent glycemic control. General parent-adolescent relationships were assessed via the Parent-Adolescent Relationship Questionnaire (PARQ), and Type I diabetes-specific psychological adjustment was assessed via the Teen Adjustment to Diabetes Scale (TADS). Questionnaires were given at baseline, at posttreatment (3 months) and at 6 and 12 months after treatment ended.
Notes	
Allocation concealment	B

Study	**Xiong 1994**
Methods	Random allocation not otherwise specified.
Participants	63 DSM-III-R Chinese schizophrenic patients living with family members.
Interventions	Standard care (medication prescription at hospital discharge plus laissez faire follow-up on patient's or family's initiative) vs. a family based intervention that included monthly 45 minute counselling sessions focussed on the management of social and occupational problems, medication management, family education, family group meetings, and crisis intervention.
Outcomes	Medication usage was assessed by family member reports. Time for which the patient took >50% of prescribed dosage was the measure for comparison of groups. Psychiatric outcomes were assessed at six, 12, and 18 months following hospital discharge by observers who were trained clinical researchers, blinded to study group allocation.
Notes	
Allocation concealment	B

Study	**Zhang 1994**
Methods	Random allocation not otherwise specified.
Participants	Men discharged after their first admission to the hospital for schizophrenia. Schizophrenia was defined according to the Chinese Medical Association criteria. Inclusion criteria were no serious concurrent medical

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	illnesses, living within commuting distance of the hospital, and willingness to attend regular family intervention sessions. Mean age for the 78 men who were followed was 24 years. Occupation was the only baseline characteristic that was not the same in each group.
Interventions	Men in both groups came to the outpatient department by their own choice; no regular appointments were made and there was no routine follow-up. Medication was obtained at these visits. Families and patients in the family intervention group were assigned to one of two counsellors for their ongoing care, were invited to come to a discharge session that focussed on education about the management of the patient's treatment, asked to come to a family group counselling session with other families three months after discharge, and then attend three-monthly group sessions with other families with similar patient problems. Non-attendance triggered a visit from study staff. Each family was contacted at least once during the 18-month follow-up. Control group patients received no family interventions.
Outcomes	All patients were seen every three months by staff physicians, blinded to the group assignment, where medication status and adherence were assessed. Adherence was defined as taking at least 33% of dose prescribed at the time of the index discharge for at least six days/week. Non-adherence was anything else. Readmission to hospital and the mean hospital free period for those who were readmitted were the treatment outcomes assessed.
Notes	
Allocation concealment	B

Study	**van Es 2001**
Methods	Patients were randomly allocated to either usual care by a paediatrician (control group) or the intervention programme (experimental group). Randomization was stratified according to hospital. Allocation was concealed. Due to the nature of the intervention, paediatricians and patients were not blinded.
Participants	The criteria for inclusion were: asthma diagnosed by a physician, treatment prescribed by a paediatrician with daily inhalation of prophylactic asthma medication during a preceding period of at least two months, between 11-18 years of age, attending secondary school, and the ability to fill in a questionnaire in Dutch.
Interventions	Control Group: All patients received usual care from the paediatricians, who were instructed to provide the same care as they normally gave to adolescent patients with asthma. Patients visited the paediatrician every four months. The paediatricians agreed not to refer participants in the control group to an asthma nurse. Experimental Group: Patients in this group received the same usual care from a paediatrician every four months. During these visits the paediatrician also discussed an asthma management zone system with the participants. This system has been developed to instruct patients about disease characteristics, triggers for airway obstruction and treatment objectives. The paediatricians also discussed the PEF measurements which the participants had registered during the two weeks preceding the visit to the paediatrician. Furthermore, the 4 visits to the paediatrician were each combined with a visit to an asthma nurse. The asthma nurses discussed several aspects of the disease individually with the participants, making use of drawings and written information. Every participant also participated in three group sessions, which took place once a week after the 3 individual sessions with the asthma nurse had taken place. After the 3 group sessions were completed, a fourth individual visit to the asthma nurse took place. The participants also received a written summary of the group sessions they had attended. Each individual session with the asthma nurse lasted approx. 30 minutes and each group session was 90 minutes. The various sessions of the intervention programme were spread out over a period of one year. During the second year, all patients in both control and intervention groups received the same usual care from their paediatrician.
Outcomes	Measurement of Compliance: Self-reported adherence was assessed by asking participants to score their adherence on a 1 to 10-point scale (range: 1-never take the meds, 10 -always takes prophylactic meds as prescribed). Expert-reported adherence was assessed by asking the participant's physician to rate the adherence of the patients on a visual analogue scale (VAS) on a 100% scale. The physicians were asked to estimate the adherence of the patient during the previous two months. Measurement of Clinical Health Outcomes: Lung function was measured via FEV. Subjective severity of asthma was assessed by asking the participant one question with a 5-point scale (1-not at all bothered,

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Characteristics of included studies (*Continued*)

	no symptoms 5 -severely bothered, unable to function). Morbidity variables (# admissions to hospital, # prescriptions or oral steroids for an exacerbation) were also recorded.
Notes	
Allocation concealment	A

Characteristics of excluded studies

Azrin 1998	Only 2 months of follow-up
Banet 1997	No measure of compliance with medication at baseline.
Bass 1986	Confounded comparison groups
Begley 1997	No specific disease/disorder being treated. No specific medication. No specific measure of treatment outcome.
Berg 1997	Study duration too short.
Bertakis 1986	Follow-up too short or on less than 80% of participants
Binstock 1986	Missing data on adherence
Birrer 1984	Follow-up too short or on less than 80% of participants
Bisserbe 1997	Study duration too short
Bodsworth 1997	No compliance data presented and < 80% follow-up
Brodaty 1983	Follow-up too short or on less than 80% of participants
Brown 1987	Missing description of disease outcome
Brown 1997b	No measure of compliance with medications
Cantor 1985	Follow-up too short or on less than 80% of participants
Cargill 1992	Follow-up too short or on less than 80% of participants
Celik 1997	Follow-up in < 80%
Cheung 1988	Confounded comparison groups
Clarkin 1998	Less than 80% follow-up
Cochran 1984	38 patients were randomized, before consent. When consent was requested, only 28 (74%) agreed so that the maximu, follow-up was less than 80%. 2 additional patients dropped out following giving consent.
Cockburn 1997	Follow-up in < 80%
Daley 1992	Missing description of disease outcome
Demyttenaere 1998	Study too short duration
Edworthy 1999	Follow-up too short (only 8 weeks)
Elixhauser 1990	Follow-up too short or on less than 80% of participants
Eron 2000	Regimen/follow-up too short (only 16 weeks for HIV therapy)
Eshelman 1976	Follow-up too short or on less than 80% of participants
Falloon 1985	Missing data on adherence
Feinstein 1959	Confounded comparison groups
Fennell 1994	Confounded comparison groups
Finney 1985	Follow-up too short or on less than 80% of participants
Gabriel 1977	Missing description of disease outcome

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Characteristics of excluded studies (*Continued*)

Garnett 1981	Missing description of disease outcome
Gibbs 1989	Missing description of disease outcome
Goodyer 1995	Follow-up too short or on less than 80% of participants
Haubrich 1999	Less than 80% follow-up at 6 months
Heard 1999	In addition to 3 asthma clinic sessions, a GP consultation (where meds could be altered?) was added to the intervention group. Also, it is unclear whether medication adherence is actually mesured (i.e. paper only states that 'medication use; is assessed)
Hornung 1998a	Patients initially randomized into treatment groups. However, these groups were re-arranged (not randomly) for the purposes of analysis.
Jameson 1995	Confounded intervention group (combined adherence intervention with adjustments to medications)
Johnson 1997	Study too short duration
Kelly 1988	Follow-up too short or on less than 80% of participants
Kelly 1990	Follow-up too short or on less than 80% of participants
Kelly 1991	Follow-up too short or on less than 80% of participants
Leenan 1997	Study too short duration
Levesque 1983	Confounded comparison groups
Levine 1979	Missing data on adherence
Lewis 1984	Follow-up too short or on less than 80% of participants
Linkewich 1974	Missing description of disease outcome
Linszen 1996	Follow-up too short or on less than 80% of participants
Lopez-Vina 2000	Follow-up less than 80%
Maiman 1978	Missing description of disease outcome
Maslennikova 1998	Confounded: patients in education group also visited 'super-specialist' doctors, while the control group received no eduation and also only visited regular primary doctors. Therefore, can't separate effects of the education from the effects of having different physicians.
Matsuyama 1993	Follow-up too short or on less than 80% of participants
Mazzuca 1986	Follow-up too short or on less than 80% of participants
McCrindle 1997	Study duration too short
McFarlane 1995	Follow-up too short or on less than 80% of participants
Miklowitz 2000	Less than 80% follow-up
Miller 1990	Follow-up too short or on less than 80% of participants
Morisky 1980	Follow-up too short or on less than 80% of participants
Morisky 1983	Missing data on adherence
Morisky 1990	Missing description of disease outcome
Mundt 2001	Less than 80% follow-up at 6 months
Murray 1993	Missing description of disease outcome
Myers 1984	Follow-up too short or on less than 80% of participants
Myers 1992	Follow-up too short or on less than 80% of participants
Nessman 1980	Follow-up too short or on less than 80% of participants
Ngoh 1997	No measure of treatment outcome reported
Nides 1993	Follow-up too short or on less than 80% of participants
O'Connor 1996	Non-randomised trial

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Characteristics of excluded studies (*Continued*)

Phan 1995	Follow-up too short or on less than 80% of participants
Putnam 1994	Follow-up too short or on less than 80% of participants
Raynor 1993	Missing description of disease outcome
Razali 1997	Compliance measured to determine eligibility, but not measured through the course of the study
Rehder 1980	Follow-up too short or on less than 80% of participants
Rettig 1986	Follow-up too short or on less than 80% of participants
Rich 1996	Follow up too short or on less than 80% of participants
Rigsby 2000	Follow up less than 6 months, and trial is not definitively negative since there are less than 50 patients per group
Rimer 1987	Follow-up too short or on less than 80% of participants
Robinson 1986	Follow-up too short or on less than 80% of participants
Roy-Byrne 2001	Confounded" part of intervention included pharmacotherapy with a SSRI, whereas usual care patients received 'treatment as usual' from their physician. Therefore, control and intervention groups may have different drug regimens.
Sanmarti 1993	Missing description of disease outcome
Saunders 1991	Follow-up too short or on less than 80% of participants
Schwartz 1981	Confounded comparison groups
Sclar 1991	Missing description of disease outcome
Seggev 1998	Less than 80% follow-up (78.8%)
Sellors 1997	No treatment outcome measured
Sharpe 1974	Missing description of disease outcome
Shepard 1979	Missing data on adherence
Shetty 1997	No random assignment to treatment groups.
Simkins 1986	Missing description of disease outcome
Smith 1986	Missing description of disease outcome
Solomon 1988	Missing description of disease outcome Follow-up too short or on less than 80% of participants
Solomon 1997	Study too short duration
Taggart 1981	Follow-up too short or on less than 80% of participants
Takala 1979	Missing data on adherence
Tapanya 1997	Study too short duration
Tinkelman 1980	Confounded comparison groups
Trienekens 1993	Confounded comparison groups
Vander Stichele 1992	Follow-up too short or on less than 80% of participants
VeldhuizenScott 1995	Follow-up too short or on less than 80% of participants
Vestergaard 1997	No treatment outcome reported
Vetter 1999	No compliance intervention, since patients in control group received clarithromycin 250 mg twice daily, while patients in intervention group received clarithromycin 500mg (modified release) once daily PLUS placebo
Vrijens 1997	Study duration too short
Wasilewski 2000	Confounded: different medications and different medication schedule in intervention and control groups
Webb 1980	Confounded comparison groups.
Williams 1986	Missing description of disease outcome

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Characteristics of excluded studies (*Continued*)

Windsor 1990	Missing description of disease outcome
Wise 1986	Follow-up too short or on less than 80% of participants
Wong 1987	Missing description of disease outcome
Xiang 1994	Follow-up too short or on less than 80% of participants
Zarnke 1997	Study too short duration

GRAPHS

Comparison 01. Studies That Met Criteria

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Adherence and Outcome			Other data	No numeric data

INDEX TERMS

Medical Subject Headings (MeSH)

Drug Therapy; Patient Compliance; Patient Education; Prescriptions, Drug; Randomized Controlled Trials; Self Administration

Medical MeSH check words

Humans

COVER SHEET

Title	Interventions for helping patients to follow prescriptions for medications
Authors	Haynes RB, McDonald H, Garg AX, Montague P
Contribution of author(s)	RBH - oversight and involvement in all stages of the review, including its 2002 update HPM - involved in all stages of review for the 2002 update PM - involved in all stages of review for the 1998 update AXG - involved in reviewing references from literature searches for relevance and for calculating agreement statistics
Issue protocol first published	1999/3
Review first published	1999/3
Date of most recent amendment	22 October 2004
Date of most recent SUBSTANTIVE amendment	08 February 2002
What's New	Fourteen new studies have been added, bringing to 33 the number of randomized trials meeting our criteria for testing interventions for helping patients to follow prescribed, self administered medications. Despite the new studies, conclusions remain the same: Most people do not follow self-administered medical treatments as prescribed and interventions to help them follow treatments are marginally effective at best, especially for long-term medical regimens. Strategies that appear to have some effect for long-term regimens involve combinations of counselling, reminders, self-monitoring and feedback, and supportive care. For short-term treatments, high adherence can be achieved by simpler means, including reminders and instruction about the importance of taking all doses.

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Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	15 August 2001
Date authors' conclusions section amended	08 February 2002
Contact address	Prof R.Brian Haynes Professor and Chair Clinical Epidemiology and Biostatistics McMaster University Medical Centre HSC Room 2C10b Hamilton L8N 3Z5 CANADA Telephone: +1 905 525 9140 E-mail: bhaynes@fhs.csu.mcmaster.ca Facsimile: +1 905 577 0017
DOI	10.1002/14651858.CD000011
Cochrane Library number	CD000011
Editorial group	Cochrane Consumers & Communication Group
Editorial group code	HM-COMMUN

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Table 01. Adherence and Outcome

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
Bailey 1990	asthma	pamphlet, workbook, counselling, phone follow-up, support group, and reinforcement of adherence (n=132)	instructional pamphlet alone (n=135)	yes	yes
Baird 1984	hypertension	once daily metoprolol (n=196)	twice daily metoprolol (n=193)	yes	no
Becker 1986	hypertension	special "reminder" pill packaging (n=86)	separate vials for each medication (n=85)	no	no
Brown 1997a	hyperlipidemia and coronary artery disease	controlled release niacin bid (n=31)	regular niacin qid (n=31)	yes	yes
Brus 1998	Rheumatoid Arthritis	Six patient education meetings. The education programme focused on compliance with sulphasalazine therapy, physical exercises, endurance activities (walking, swimming, bicycling), advice on energy conservation, and joint protection. Four (two hour) meetings were offered during the first months. Reinforcement meetings were given after four and eight months. The programme was implemented in groups and partners were invited to attend the meetings. (n=29)	The control group received a brochure on RA, as provided by the Dutch League against Rheumatism. This brochure gives comprehensive information on medication, physical and occupational therapy. (n=31)	no	no
Chaplin 1998	schizophrenia	individual semi-structured educational sessions	Usual care (n=28).	no	no

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Table 01. Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
		discussing the benefits and adverse effects of antipsychotic drugs, including tardive dyskinesia (n=28).			
Colcher 1972	strep throat	special counselling and written instructions on need to take all pills (n=100)	usual care (n=100)	yes	yes
Cote 1997	asthma	extensive asthma education program plus written self-managed action plan based on PEF (n=50) or based on asthma symptom monitoring (n=45)	basic information provided plus verbal action plan could be given by physician (n=54)	no for each intervention	no for each intervention
Friedman 1996	hypertension	telephone-linked computer system (TLC) - an interactive computer-based telecommunications system that converses with patients in their homes between office visits to their physicians (n=156)	regular medical care (n=145)	yes	yes
Gallefoss 1999b	Asthma & COPD	An educational intervention consisting of a specially constructed patient brochure, two 2-hour group sessions (separate groups for asthmatics and patients with COPD) concentrating on pathophysiology, antiobstructive medication, symptom awareness, treatment plans, and physiotherapy. One or two	Usual care from GP (39 asthmatics, 32 COPD patients)	no	no

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Table 01. Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
		40-min individual sessions were supplied by both a nurse and a physiotherapist. At the final teaching the patients received an individual treatment plan on the basis of the acquired personal information and 2 wk of peak flow monitoring. (n=39 asthmatics, 32 COPD patients)			
Girvin 1999	Hypertension	Enalapril 20mg od (n=27)Cross-over study, with 4 week study periods	Enalapril 10mg bid (n=27)Cross-over study	yes	no
Haynes 1976	hypertension	tailoring, self-monitoring of pills and blood pressure, rewards for higher adherence and lower blood pressure (n=20)	usual care (n=18)	yes	no
Henry 1999	H. Pylori infection	10 days of omeprazole 20mg bd, amoxicillin 500mg tds and metronidazole 400 mg tds, verbal advice on medication use and its possible side effects in an initial 20 minute consultation. Patients also received medication in dose-dispensing units, an information sheet on H. Pylori treatment, and a medication chart. Compliance in intervention group patients was also	10 days of omeprazole 20mg bd, amoxicillin 500mg tds and metronidazole 400 mg tds, verbal advice on medication use and its possible side effects in an initial 20 minute consultation. (n=59)	no	no

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Table 01. Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
		encouraged by a phone call 2 days after the start of therapy. (n = 60			
Howland 1990	acute infections	warnings about potential adverse effects of drugs (n=50)	no warnings about adverse effects of drugs (n=48)	no	no
Johnson 1978	hypertension	a. self-monitoring of blood pressure at home (n=34) b. monthly home visits by a research assistant (n=33) c. both a and b (n=35)	neither intervention (n=34)	no for each intervention	no for each intervention
Katon 2001	Depression	Patient education, 2 visits with a depression specialist, telephone monitoring and follow-up (n= 194)	Usual care (n=192)	Yes	Yes for SCL-20 scores and depressive symptomsNo for episodes of relapse/ recurrence
Kemp 1996	Acute psychosis.	4-6 session compliance therapy that focused on illness, conceptualisation of the problem, symptoms, side effects of treatment, and the stigma of drug treatment (n=25)	4-6 session nonspecific counselling (n=22)	yes	yes for global functioning assessment yes for full version of the brief psychiatric rating scale no for the abridged version of the brief psychiatric rating scale no for dose of antipsychotic drug
Kemp 1998	psychotic disorders	4-6 session compliance therapy that focused on illness, conceptualisation of the problem, symptoms, side effects of treatment, and the stigma of drug treatment (n=39)	4-6 session nonspecific counselling (n=35)	yes, at 12 months.	no, at 12 months, for the 7-item version of the Brief Psychiatric Rating Scale. yes, at 12 months, for the Global Assessment of Function. yes, at 6 months, for the Schedule for Assessment of Insight.

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Knobel 1999	HIV	Zidovudine+ lamivudine + indinavir PLUS individualised counselling/ assessments which consisted of adaptation of treatment to the patient's lifestyle and detailed information about highly active antiretroviral therapy (n=60)	Zidovudine+ lamivudine + indinavir plu conventional care (n=120)	yes	Yes for reduction of viral load No for detectable viral load.
Levy 2000	Acute Asthma	1 hour structured asthma consultation with study nurse 2 weeks after entry into study, followed by 2 or more 30 minute consultations at 6-weekly intervals (n=103).	Usual care (n=108)	Yes for use of inhaled topical steroids and rescue medication for severe attacksNot statistically significant for use of inhaled topical steroids and rescue medication for mild attacks	yes
Logan 1979	hypertension	worksite care by nurses, tailoring of medications to daily schedule, self-monitoring of blood pressure, rewards for higher adherence and lower blood pressure (n=232)	usual care at doctor's office (n=225)	yes	yes
Merinder 1999	Schizophrenia	8-session psychoeducational programme for schizophrenic patients and their relatives, conducted using a mainly didactic interactive method (n=23)	Usual treatment provided in community psychiatry (n=23)	no	Yes for knowledge of schizophrenia and for VSSS subscore satisfaction with relatives' involvement. There was also a trend towards reduced BPRS score in intervention group (p=0.07). No for time to relapse or insight into psychosis or psychosocial function (GAF)
Peterson 1984	epilepsy	counselling, leaflet, self-monitoring of pill taking and seizures, mailed reminders for appointments and missed drugs refills (n=27)	usual care (n=26)	yes	no

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Peveler 1999	Depression	Treatment information leaflet (n=53), drug counseling (n=52) or both leaflet and counseling (n=53)	Usual care (n=55)	yes for counseling (at 12 weeks) No for leaflet	no for counseling No for leaflet
Piette 2000	Diabetes	Automated telephone assessment and self-care education calls with nurse follow-up (n=137)	Usual care (n=143)	yes	yes
Razali 2000	Schizophrenia	Culturally modified family therapy (CMFT), which consists of a sociocultural approach of family education, drug intervention programme and problem-solving skills (n=80).	Behavior Family Therapy (BFT) (n=86)	yes	no at 6 months Yes at 12 months for all variables (Exacerbation, GAF score, SBS score, Rehospitalization, Family Burden)
Sackett 1975	hypertension	a. care at worksite by occupational health physicians (n=37) b. detailed "programmed" instructions about hypertention and adherence (n=28) c. both a and b (n=44)	neither intervention (n=25)* * numbers provided by author	no	no
Strang 1981	schizophrenia	family therapy (n=17)	individual supportive therapy (n=15)	yes	yes
Tuldra 2000	HIV	Psychoeducative intervention to implement adherence. i.e explanations about reasons for starting treatment and the relevance of appropriate adherence, development of a dosage schedule with patients' input, patients were taught how to manage various other aspects of medication taking in HAART (i.e. forgetting, side effects, changes in daily	Usual medical follow-up (n=61)	no	no

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Table 01. Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
		routine). Phone number was given should patients have any questions before next interview. Verbal reinforcement of adherence at follow-up visits. (n=55)			
Wysocki 2001	Diabetes	Behavioral-Family Systems Therapy (BFST) -10 sessions consisting of 4 therapy components: problem solving training, communication skills training, cognitive restructuring and functional and structural family therapy, plus $100 monetary incentive for attending all 10 intervention sessions. (n=38)Education and Support (ES) - families attended 10 group diabetes education and social support meetings (45 minute educational presentation by diabetes professional + 45 min interaction among the families), plus $100 monetary incentive for attending all 10 intervention sessions.(n=40).	Current Therapy (n=41) - standard pediatric endocrinology follow-up and self-management training.	No for BFST and ES at posttreatmentYes for BFST at 6 and 12-monthsNo for ES at 6 and 12-months	No for BFST in diabetic control or adjustment to diabetesYes for BFST on PARQ scales at posttreatment, 6 and 12 months.No for ES
Xiong 1994	schizophrenia	family counselling and close follow-up (n=34)	prescription of medication without formal follow-up (n=29)	no	yes
Zhang 1994	schizophrenia	family intervention (n=42)	prescription of medication	no	yes

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Table 01. Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
			without formal follow-up (n=41)		
van Es 2001	Asthma	Usual care + pediatrician discussed "asthma management zone system" with participants + pediatrician discussed PEF readings from prior 2 weeks + 4 individual sessions with the asthma nurse + 3 educational group sessions with asthma nurse (n= 58)	Usual care - pediatrician every 4 months (n=54)	No at T1 (12 months) Yes for self-reported adherence at T2 (24 months) (but follow-up was only 77% at this time, so doesn't count)	no