Interventions for enhancing medication adherence (Review)

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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 of prescribed medications, but also might increase their adverse effects.

Objectives
To update a review summarizing the results of randomized controlled trials (RCTs) of interventions to help patients follow prescriptions for medications for medical problems, including mental disorders but not addictions.

Search strategy
We updated searches of *The Cochrane Library,* MEDLINE, CINAHL, EMBASE, International Pharmaceutical Abstracts (IPA), PsycINFO (all via OVID) and Sociological Abstracts (via CSA) in January 2007 with no language restriction. We also reviewed bibliographies in articles on patient adherence and articles in our personal collections, and contacted authors of relevant original and review articles.

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
Study design features, interventions and controls, and results were extracted by one review author and confirmed by at least one other review author. We extracted adherence rates and their measures of variance for all methods of measuring adherence in each study, and all outcome rates and their measures of variance for each study group, as well as levels of statistical significance for differences between study groups, consulting authors and verifying or correcting analyses as needed. The studies differed widely according to medical condition, patient population, intervention, measures of adherence, and clinical outcomes. Therefore, we did not feel that quantitative analysis was scientifically justified; rather, we conducted a qualitative analysis.

Main results
For short-term treatments, four of ten interventions reported in nine RCTs showed an effect on both adherence and at least one clinical outcome, while one intervention reported in one RCT significantly improved patient adherence, but did not enhance the clinical outcome. For long-term treatments, 36 of 81 interventions reported in 69 RCTs were associated with improvements in adherence, but only 25 interventions led to improvement in at least one treatment outcome. 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, counseling, family therapy, psychological therapy, crisis intervention, manual telephone follow-up, and supportive care. Even the most effective interventions did not lead to large improvements in adherence and treatment outcomes.

Authors' conclusions
For short-term treatments several quite simple interventions increased adherence and improved patient outcomes, but the effects were inconsistent from study to study with less than half of studies showing benefits. Current methods of improving adherence for chronic

health problems are mostly complex and not very effective, so that the full benefits of treatment cannot be realized. High priority should be given to fundamental and applied research concerning innovations to assist patients to follow medication prescriptions for long-term medical disorders.

PLAIN LANGUAGE SUMMARY

Interventions for enhancing adherence to prescribed medications

Many people do not take their medication as prescribed. Our review considered trials of ways to help people follow prescriptions. For short-term drug treatments, counseling, written information and personal phone calls helped. For long-term treatments, no simple intervention, and only some complex ones, led to improvements in health outcomes. They included combinations of more convenient care, information, counseling, reminders, self-monitoring, reinforcement, family therapy, psychological therapy, mailed communications, crisis intervention, manual telephone follow-up, and other forms of additional supervision or attention. Even with the most effective methods for long-term treatments, improvements in drug use or health were not large. Several studies showed that telling people about adverse effects of their medications did not affect their use of the medications.

BACKGROUND

Patient adherence and adherence are synonyms. 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, his / her adherence would be (10 / 28 =) 36%. The term, adherence, is intended to be non-judgmental, a statement of fact rather than of blame of the patient, prescriber, or treatment. Adherence is not the same as "concordance", which includes a consensual agreement about treatment taking established between patient and practitioner.

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, poor memory, and 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. Burke 1997; Haynes 1979a; Houston 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 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; Haynes 1999; McDonald 2002, Haynes 2005). We found inconsistent evidence of effects on adherence, and even more limited evidence of effects on patient outcomes.

The current version of our review updates our 2005 version (Haynes 2005, which included 57 trials) with 21 new studies (Andrade 2005; Bailey 1999; Beaucage 2006; Collier 2005; Ellis 2005; Hederos 2005; Howe 2005; Lee 2006; MarquezContreras2005; MarquezContreras2006; Odegard 2005; Portsmouth 2005; Remien 2005; Rickles 2005; Rudd 2004; Sadik 2005; Samet 2005; Schroeder 2005; Van Servellen 2005; Vergouwen 2005; Yopp 2004).

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 summarize all unconfounded randomized 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

Randomized controlled trials (RCTs) that provided unconfounded

tests of interventions expected to affect adherence. A confounder is a characteristic that is extraneous to the question being addressed in the study, but which can influence the outcome and is unequally distributed between the exposure groups being compared (Sinclair 1992). 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 adherence effects of this regimen. Thus, only the unconfounded comparison of instructions for phenoxymethyl penicillin was included in the review.

Types of participants

Patients who were prescribed medication for a medical (including psychiatric) disorder, but not for addictions.

Types of intervention

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

Types of outcome measures

We reviewed original studies 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 METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Consumers and Communication Group methods used in reviews.

We searched: *The Cochrane Library,* MEDLINE, CINAHL, EMBASE, International Pharmaceutical Abstracts (IPA), PsycINFO (all via OVID) and Sociological Abstracts (via CSA). We completed database searches for relevant articles on February 1, 2007, updating previous searches that were undertaken on: September 1, 1993; December 12, 1993; June 1, 1994; June 30, 1995; February 28, 1997; July 31, 1998; August 15, 2001; and September 30, 2004. All databases were originally searched from their start date.

The search strategy of the MEDLINE and CINAHL 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 PsycINFO 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 Sociological Abstracts search strategy was as follows: ((patient or treatment or dropouts) AND (clinical trials or control) AND (drugs or medicine)).

The International Pharmaceutical Abstracts (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.

We conducted an additional search of the EMBASE database for citations in any language, 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)).

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

METHODS OF THE REVIEW

Each full text article was reviewed independently by at least two of the review authors according to the criteria for review (see 'Criteria for considering studies for this review'), 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 in any formulation (tablets, liquid, injectables, and so on), 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 of follow-up for studies with positive initial findings. Disagreements (primarily of assessment of confounding and adequacy of follow-up) were resolved by discussion.

For each eligible study, one review author extracted study design features, features of the interventions and controls, and the results, and the extraction was reviewed and confirmed by at least one other review author. We extracted adherence rates and their measures of variance for all methods of measuring adherence in each study, and all outcome rates and their measures of variance for each study group, as well as levels of statistical significance for differences between study groups. We reviewed other articles on the same project for details and contacted authors for missing, incomplete or unclear methods or data, and verified or corrected analyses as needed. We also assessed whether randomization was concealed, according to the Cochrane Handbook for Systematic Reviews of Interventions procedure (Higgins 2005). If allocation concealment was unclear, where possible we consulted with the study author. The studies differed widely according to medical condition, patient population, intervention, measures of adherence, and clinical outcomes. Therefore, we did not feel that quantitative analysis was scientifically justified; rather, we conducted a qualitative analysis.

Consumer participation

No consumer referees were involved in the editorial process for the 2007 update of this review.

DESCRIPTION OF STUDIES

The most recent (January 2007) searches of all sources retrieved a total of 5806 citations (including 46 review articles), 65 of which were judged to merit scrutiny of the full articles. Twenty of the latter met all review criteria, testing 22 unconfounded interventions in 20 new trials (references as noted in Background). In addition, a study that was awaiting assessment in the last update of the review (Bailey 1999) was included in this update after further examination.

Thus, to date, searches have retrieved a total of 18,867 citations (including 504 review articles), 1020 of which were judged to merit scrutiny of the full articles. Eighty-two citations describing 78 trials (Gallefoss 1999 was described in two papers; Ludman 2003 and Von Korff 2003 provided supplementary information for the study described by Katon 2001) met all review criteria, testing 89 unconfounded interventions.

Key features of these 78 trials are summarized in the 'Other Data' table. A narrow range of disorders was studied for long-term conditions. Numbers of participants in the table refer to those allocated to each study group, rather than the number included in the analyses. This is because some articles did not indicate how many were lost to follow-up for each group; rather, they state an overall percentage that remained at the end of the study period. As per our study criteria, this was at least 80% in each study. These included: eleven studies in hypertension; ten in schizophrenia or acute psychosis; eleven in asthma (and / or chronic obstructive pulmonary disease (COPD)); two in rheumatoid arthritis; one in epilepsy; three in hyperlipidemia; one in ischaemic heart disease; one in heart failure; one in hypertension and hyperlipidemia; four in depression; twelve in human immunodeficiency virus (HIV); six in diabetes; one in tuberculosis; one in oral anticoagulant therapy; one in contraception; and two studies concerning complex regimens in the elderly. Only nine studies concerned short-term conditions, acute infections in all cases; namely, three for Helicobacter-pylori infection, two for bacterial and/or viral infections, one for seasonal rhinitis and asthma, one for Streptococcal pharyngitis, one for malaria, and one for macrolide antibiotics.

Of the 21 new studies, only one study assessed an acute disorder - acute infections (Beaucage 2006). The remaining 20 new studies evaluated chronic conditions, including HIV infection (Andrade 2005; Collier 2005; Portsmouth 2005; Remien 2005; Samet 2005; Van Servellen 2005); hypertension (MarquezContreras2005; MarquezContreras2006; Rudd 2004; Schroeder 2005); diabetes (Ellis 2005; Howe 2005; Yopp 2004; Odegard 2005); heart failure (Sadik 2005); depression (Rickles 2005; Vergouwen 2005); hypertension and hyperlipidemia (Lee 2006); and asthma (Bailey 1999; Hederos 2005). Among the 21 new studies, hypertension combined with hyperlipidemia, and heart failure, 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 insufficient common ground for quantifying differences between groups or calculating effect sizes that would permit quantitative summarization 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. However, as noted in the text descriptions of studies below, some of the negative results were unconvincing because of the small numbers of participants studied (i.e. low statistical power).

METHODOLOGICAL QUALITY

Some trials, or arms of trials, did not meet our criteria because of confounding (see table 'Characteristics of excluded studies'); for example, an arm of the Colcher study (Colcher 1972), as described in 'Types of Studies'.

Before July 1998, none of the studies from previous reviews clearly dealt with 'concealment of allocation', intended to prevent 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 minimization that they used was "immune to experimental bias." From August 1998 until September 30, 2004, 14 studies (36% of the 39 eligible articles) reported concealment of allocation. In the latest update (until February 1, 2007), 6 of 21 new studies reported concealment of allocation, so this marker of quality does not appear to be improving in the most recent studies.

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.

RESULTS

Many diverse interventions were tested. No taxonomy of simple labels would do justice to the often complex interventions tested (which we have attempted to summarize in the table 'Characteristics of included studies'), but the following common themes and groupings suggest themselves:

a) more instruction for patients, e.g. verbal, written, or visual material (Bailey 1999; Becker 1986; Brus 1998; Canto De Cetina 2001; Colcher 1972; Cote 1997; Farber 2004; Gallefoss 1999; Ginde 2003; Henry 1999; Katon 2001; Laporte 2003; Levy 2000; MarquezContreras04a; Merinder 1999; Peveler 1999; Schaffer 2004; van Es 2001); programmed learning (Sackett 1975); and formal education sessions (Howe 2005; Van Servellen 2005);
b) counseling about the patients' target disease, the importance of therapy and compliance with therapy, the possible side-effects, patient empowerment, couple-focused therapy to increase social support (Al-Eidan 2002; Bailey 1999; Cote 2001; Gani 2001; Hill 2001; Kemp 1996; Kemp 1998; Morice 2001; O'Donnell 2003; Pradier 2003; Ran 2003; Rawlings 2003; Razali 2000; Remien 2005; Rudd 2004; Stevens 2002; Tuldra 2000; Vergouwen 2005; Wysocki 2001);
c) automated telephone, computer-assisted patient monitoring and counseling (Friedman 1996; Piette 2000);
d) manual telephone follow-up (Al-Eidan 2002; Collier 2005; Farber 2004; Howe 2005; Katon 2001; MarquezContreras04a; MarquezContreras2005; Stevens 2002);
e) family intervention (Merinder 1999; Ran 2003; Razali 2000; Strang 1981; Xiong 1994; Zhang 1994);
f) various ways to increase the convenience of care, e.g. provision at the worksite or at home (Berrien 2004; Haynes 1976; Nazareth 2001; Peterson 2004; Sackett 1975);
g) simplified dosing (Baird 1984; Brown 1997a; Girvin 1999; Portsmouth 2005);
h) involving patients more in their care through self-monitoring of their blood pressure (Haynes 1976; MarquezContreras2006), seizures (Peterson 1984) or respiratory function (Bailey 1990; Cote 1997; Morice 2001);
i) reminders, e.g. programmed devices (Andrade 2005), and tailoring the regimen to daily habits (Haynes 1976; Knobel 1999; Sackett 1975);
j) special 'reminder' pill packaging (Becker 1986);
k) dose-dispensing units of medication and medication charts (Al-Eidan 2002; Henry 1999);
l) appointment and prescription refill reminders (Peterson 1984);
m) reinforcement or rewards for both improved adherence and treatment response, e.g. reduced frequency of visits and partial payment for blood pressure monitoring equipment (Haynes 1976);
n) different medication formulations, such as tablet versus syrup (Ansah 2001);
o) crisis intervention conducted when necessary, e.g. for attempted suicide, aggressive and destructive behaviour (Ran 2003);
p) direct observation of treatments (DOTS) by health workers or family members (Walley 2001);
q) lay health mentoring (Coull 2004);
r) augmented pharmacy services (Andrade 2005; Beaucage 2006; Lee 2006; Odegard 2005; Rickles 2005; Sadik 2005; Volume 2001; Weinberger 2002);
s) psychological therapy, e.g. cognitive behaviour therapy, multisystemic therapy (Ellis 2005; Pradier 2003; Weber 2004; Yopp 2004);
t) mailed communications (MarquezContreras2005); and
u) group meetings (Bailey 1999; Hederos 2005; Schroeder 2005).

Detailed information about each trial is included in the Adherence and Outcome table (Table 1) with salient features described below. The available evidence did not include direct comparisons of the strategies listed above, and more than one strategy was often included in an intervention, so this taxonomy is simply a descriptive guide, and not used for the analysis that follows. These groupings are broad to enable readers to organize studies as best suits their purpose for the review.

Less than half of the interventions tested (41 of 92 interventions: 5 for short-term treatments and 36 for long-term treatments) in the 78 studies were associated with statistically significant increases in medication adherence and only 30 of 92 interventions reported statistically significant improvements in treatment outcomes (4 for short-term treatments and 26 for long-term treatments). Most of the studies were quite small, however, and the possibility of a false-negative (beta) error was quite high.

Short-term treatments

For short-term treatments, we did not find enough studies on any individual disease condition to permit grouping by disease. A study testing an intervention to increase adherence with a regimen for streptococcal pharyngitis (Colcher 1972) reported success with a relatively simple maneuver of counseling 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. The investigators concluded that no harm was found for either adherence or adverse effects.

Three studies concerned Helicobacter pylori (H. pylori) treatment. Henry 1999 evaluated an intervention consisting of three components, an information sheet on H. pylori treatment (10-day course), medication in dose-dispensing units, and a medication chart, versus a usual practice control, for patients receiving medication for H. pylori eradication. There was no significant improvement in adherence 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 limiting the effect of any additional intervention. In Stevens 2002 both the intervention and control groups received blister packs with daily doses clearly marked; both groups were also counseled by a pharmacist: five minutes for the control group, and longer and more detailed for the intervention group (including a detailed review of possible side effects). The intervention group also received a follow-up phone call after two or three days of therapy. Self-report was used for measuring adherence (an insensitive method). No difference was found in adherence or H. pylori eradication, and the rates of adherence were high for both. Given the short duration of the treatment (seven days), and the provision of blister packs and counseling for both groups, the study would appear to indicate that five minutes of counseling was sufficient. Al-Eidan 2002 added counseling from a hospital pharmacist and a follow-up phone call after three days of therapy in the intervention group (including mentioning possible side-effects) for H-pylori eradication. The control patients were only given a standard advice sheet and referral to their family physician, who prescribed the same medication. Both adherence (pill count) and H. pylori eradication were improved in the intervention group compared with the control group.

Ansah 2001 investigated whether the use of pre-packed chloroquine tablets versus chloroquine syrup could improve adherence to malaria treatment for children. Adherence in the tablet group was more than twice that of the syrup group, but in 44% of cases of non-adherence in the syrup group, the problem was parents giving more than the prescribed dose. In any event, there was no difference in the clinical outcomes.

Ginde 2003 assessed whether free dispensing of azithromycin for infections in the emergency department resulted in higher adherence than providing patients with a prescription that could be filled for free at a pharmacy eight blocks away. Significantly fewer patients in the control group filled their prescription. However, there was no significant difference between the two groups in completing the course of antibiotics by patient report. Further, there was no difference in subsequent emergency room visits or hospital admissions. The treatment filling rate for the control group was based on the assumption that control patients used the participating pharmacy eight blocks away that provided the drug free of charge; patients were apparently not asked if they filled their prescription elsewhere. The 'course completed' rate was based on self-report during telephone calls, with no indication that interviewers were blinded to groups, nor was the exact question given. Technically, this study qualified for the review, but the reliability and credibility of the measures were suspect. The intervention is also impractical in any setting where giving drugs for free is not possible.

Gani 2001 separated patients with seasonal allergic rhinitis (SAR) into three groups. Patients in the group A were given nasal spray with the instructions provided by the manufacturer. Patients in the group B received a brief training on how to use the nasal spray and were given simplified written instructions on the use of the device. Patients in the group C attended a one-hour informal lesson on the clinical and pathogenic aspects of SAR, the treatment strategy, the correct use of medications, and the possible side effects of drugs. After eight weeks follow-up, the adherence in the groups B and C was statistically significantly higher than in the group A, but there was no difference between the groups B and C. The severity of symptoms during the pollen season did not differ among the three groups, but this factor was counterbalanced by the significantly higher use of rescue medications in the group A. Groups B and C had a significantly lower occurrence of asthma symptoms, as confirmed by a lower intake of bronchodilator. Thus, for patients with SAR, both interventions of training and detailed information enhanced clinical treatment outcomes.

Beaucage 2006 used a pharmacist telephone follow-up intervention (PTFI) to improve adherence to antibiotic treatment for patients who were initiating treatment with oral antibiotics. On day 3 of antibiotic treatment, a pharmacist contacted patients assigned to PTFI. The pharmacist documented the patient's condition, checked on the presence of adverse effects and on the patient's understanding of the dosage. They stressed the importance of adherence to treatment and offered encouragement. Patients were encouraged to contact the pharmacist if they had further concerns. If patients could not be reached on day 3 of antibiotic treatment, they were contacted until reached or until day 5. Adherence, measured with a pill count, was not found to be significantly different between the intervention group (n = 126) and the control group (n = 129). A count of infectious symptoms and an infection severity score were not significantly different between PTFI patients and those assigned to usual care. The authors acknowledged that patients' self-reports of infectious symptoms might not have been substantial enough to indicate a cure. To support the patients' sub-

jective reporting of symptoms, antimicrobial cultures taken before and after treatment would have been helpful.

Longer-term treatments

Dosing schedules

The following studies implemented changes in dosing schedules as a strategy for improving medication adherence. Baird 1984 randomized patients to receive either a once-daily or twice-daily dose of Betaloc (metoprolol) for patients with hypertension. While a significant difference was found for adherence rates, there was no significant improvement for clinical outcomes. 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. Adherence significantly improved in the intervention group with 95% with the controlled-release niacin versus 85% with regular niacin. There was a significant improvement in the lipid profile in the group using controlled-release niacin versus regular niacin. The controlled-release niacin was associated with fewer episodes of flushing than the regular niacin and this might have contributed to the increase in adherence and thus the better outcome. This intervention would be generalizable to those situations where a reduction in the dosing frequency is possible, while maintaining the same total dose.

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 with once-a-day dosing, but treatment outcomes were not. The difference in percentage of doses taken by pill count between the two periods was significantly in favour of the once daily regimen, as was the percentage of doses taken as measured by a pill container that recorded lid openings (Medication Event Monitoring System; MEMS), and the percentage of days with the correct number of doses taken. However, the percentage of days when no doses were taken was also significantly higher in the once daily regimen. By contrast, for treatment outcomes, there was a greater reduction in blood pressure, which almost reached statistical significance, in the twice-a-day 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 qualified for this adherence review. It should also be noted that this study was small in sample size (n = 27 per group) and may not be of sufficient power to detect improvements in clinical outcomes.

Portsmouth 2005 simplified the dose for a thymidine-based nucleoside reverse transcriptase inhibitor (NRTI) from a twice-daily to a once daily dose. Patients in the intervention group (n = 22) received d4T PRC/3TC/EFV once daily while those in the usual care group (n = 21) continued with the twice-daily regimen of d4T IR/3TC/EFV or Combivirs/EFV. MEMS caps for this drug were used to measure taking adherence, timing adherence, and correct dosing adherence. None of the measures of adherence was significantly different between groups. The intervention group did not perform better on any clinical outcome. The lack of significant results for both adherence and clinical outcomes may be due to the small sample size.

Because we found little commonality in the interventions tested for longer-term treatments other than the dosing schedules just described, we have chosen to describe the studies according to disease conditions. In doing so, we lament the limited theoretical underpinnings and lack of consistent features of most adherence interventions, point out that adherence problems are a constant feature of all medical regimens, and do not wish to imply that readers can learn only from studies for specific disease conditions they might be interested in.

Asthma and chronic obstructive pulmonary disease (COPD)

In Cote 1997 a complex intervention did not improve adherence to medications. 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, 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 adherence 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.

In a later study Cote 2001 assessed two different educational interventions for adult patients consulting with an acute asthma exacerbation. Patients in 'Group Limited Education (LE)' were given a self-action plan that was explained by the on-call physician. The action plan used 'traffic lights' (green, yellow, red) to describe specific states of asthma control based on Peak Expiratory Flow and symptoms and actions that the patient should take for each state. Patients in a 'Structured Educational Group (SE)', in addition to what patients in Group LE received, participated in a structured asthma educational program based on the PRECEDE model of health education. This model took into consideration three different issues that were important when dealing with health-related behaviours: predisposing factors (belief, attitude, knowledge), enabling factors (community resource, family support), and reinforcement. The intervention focused mainly on self-management. No significant improvements in medication adherence or in clinical outcomes between the two groups were obtained. The method of measuring adherence was very insensitive: it only indicated whether a person had a prescription for inhaled corticosteroids, not whether they used it.

Gallefoss and Bakke (Gallefoss 1999) tested an educational intervention in patients with asthma or COPD. This consisted of a

specially constructed patient brochure, and two two-hour group sessions (separate groups for asthmatics and patients with COPD). The sessions concentrated 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-minute educational sessions by a physiotherapist. The patient's pulmonary symptoms were registered and discussed with emphasis on the early symptoms experienced at exacerbations. Individual factors causing attacks / exacerbations and concerns regarding adverse effects of medication were discussed and inhalation technique was checked. At the final teaching session 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, but the difference in adherence was not quite significant when based on median adherence. A fatal flaw in the study design undermined the credibility of even these marginally positive results: participants assigned to the educational program but not attending all sessions were withdrawn from the study analysis (Gallefoss 1999, reported in the *American Journal of Respiratory and Critical Care Medicine* 1999; 160 (6) 2000-5). Thus, the results for adherence were based on follow-up of 38 of 39 control group participants but only 30 of 39 intervention group participants. Data obtained via personal contact with the authors on forced expiratory volume in 1 second (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 (i.e. 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, the power to detect improvements in adherence or clinical outcomes was very low. Finally, there were no improvements in adherence or clinical outcomes for patients with COPD, even based on the per protocol analysis.

Bailey 1999 investigated two self-management interventions to improve adherence to asthma medications in comparison to a group of patients receiving usual care. The first intervention is an asthma self-management program (ASMP) where the main component was a skill-oriented self-help workbook about asthma, asthma triggers, and asthma care services. ASMP patients (n = 78) also received a one-on-one session with an educator to discuss the workbook, concerns about asthma, and barriers to adherence. ASMP patients attended a minimum of two group sessions with other asthma patients and received a peak flow monitor to help them identify impending asthma attacks. Patients received two telephone calls and a follow-up letter at one, two, and four weeks, after the counseling session about the use of the peak flow monitor and general concerns. The second intervention was a core elements program (CEP), which included a shortened version of the asthma workbook. The workbook was reviewed in a brief (15 to 20 minutes) one-on-one session with an educator. Patients in this second intervention (n = 76) were also trained to use peak flow meters and inhalers. The two interventions were compared to a group of asthma patients receiving usual care (n = 78). Neither intervention was shown to be superior to usual care for adherence and clinical outcomes.

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 less than 77%.)

Morice and Wrench (Morice 2001) explored the role of an asthma nurse in treatment adherence and self-management. Compared with the control group, patients in the educational intervention group had a minimum of two separate sessions, lasting on average 30 minutes each. An agreed individualized self-management plan was determined, with written instructions using the 'Sheffield Asthma Card'. Each patient was given a peak flow meter to take home and instructions on monitoring, with documentation of predicted peak low measurement and parameters for altering treatment, as well as clear written guidelines on when to seek emergency care. All guidance offered throughout the educational program was based on the British Thoracic Society (BTS) guidelines for the management of asthma in adults. There were no significant improvements in adherence or clinical outcomes at six months. The small sample sizes (n = 40 for each group) limited the power of the study to differentiate between the two groups.

In a cluster randomized trial of 36 pharmacies, Weinberger 2002 investigated the effectiveness of a pharmaceutical care program for patients with asthma or COPD. The pharmaceutical care program (12 pharmacies, 447 patients) provided pharmacists with recent patient-specific clinical data (peak expiratory flow rates (PEFRs), emergency department visits, hospitalizations, and medication adherence), training, customized patient educational materials, and resources to facilitate program implementation. The PEFR monitoring control group (12 pharmacies, 363 patients) received a peak flow meter, instructions about its use, and monthly calls to elicit PEFRs. However, PEFR data of these participants were not provided to the pharmacist. Patients in a usual care group (12 pharmacies, 303 patients) did not receive peak flow meters; during monthly telephone interviews, PEFR rates were not elicited.

Pharmacists in both control groups had a training session but received no components of the pharmaceutical care intervention. There were no significant between-group differences in medication adherence or health-related quality of life (HRQOL) at six months and at one year.

Farber and Oliveria (Farber 2004) determined the effect of an asthma education and management intervention. Subjects in the intervention group (n = 28) received basic asthma education; instructions on use of a metered-dose inhaler with holding chamber; a written asthma self-management plan illustrated by zones coloured green, yellow, and red; a sample age-appropriate holding chamber; and prescriptions for medication needed to implement the plan. Three brief follow-up phone calls were placed to patients in the intervention group at one to two weeks, four to six weeks and three months after enrolment. Subjects in the control group (n = 28) received routine care in the emergency department (ED), hospital, or both, from their physicians. This study showed that a single session of educational and management intervention and three brief follow-up phone calls were not sufficient to have a major positive impact on treatment outcomes, but improvement in asthma controller medication use was reported. With its small sample size, the power of this study to detect a benefit was low.

Schaffer and Tian (Schaffer 2004) compared the effects of a theoretically-focused audiotape with a standard educational booklet on asthma preventive medication adherence and asthma outcomes. Patients were separated into 4 treatment groups: (a) standard provider education (control) (n = 13); (b) audiotape alone (n = 10); (c) National Heart Lung and Blood Institute (NHLBI) booklet alone (n = 12); and (d) audiotape plus NHLBI booklet (n = 11). The results showed a positive effect on adherence by pharmacy-refill measure (but not by self-report) for NHLBI booklet versus control, and for NHLBI booklet plus audiotape versus control, but not for audiotape versus control at six months. No therapeutic benefit was observed at six months, but, again, the small sample size meant a low power for this study.

In Hederos 2005 the intervention targeted parents of children with asthma (ages three months to six years) and consisted of three weekly meetings in a group setting with parents and another meeting six months later. The interventions were conducted by a multidisciplinary team (three pediatricians, three nurses, and two psychologists). Usual care (n = 28) consisted of education about asthma and its treatment. After 18 months, doctors' rating of very good adherence on a visual analogue scale (VAS) was in favour of the intervention group. The verified mean adherence was not significant but the verified poor adherence (score < 50) was found to be significant with the control group indicating lower adherence. Despite the positive outcomes in some measures of adherence, there were no positive outcomes for the clinical outcomes. A larger sample size would be needed to detect a clinically meaningful difference between the two groups, should one exist.

Hypertension

A study of hypertension that reported positive effects on both adherence and patient outcomes (Haynes 1979a) had an intensive intervention, including care provided at the worksite, special pill containers, counseling, reminders, self-monitoring, support groups, feedback and reinforcement, all administered by staff who were supported from study funds. Johnson 1978 used a factorial design of the following interventions in addition to usual care: self-monitoring of blood pressure only; home visits only; self-monitoring of blood pressure and home visits; or usual care. Neither intervention, nor their combination, was found to be effective at improving adherence or clinical outcomes, but the sample size was small.

Another study in hypertensive patients, Friedman 1996, tested a telephone-linked computer system (TLC) for monitoring and counseling patients. The unadjusted results did not demonstrate significant improvement in adherence 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. Further adjustment, for baseline blood pressure, resulted in a significant improvement in diastolic blood pressure in the TLC group but no difference between the groups for systolic blood pressure. Sub-group analysis showed, in people who were non-adherent at baseline (n = 26), that those using TLC had significantly greater improvement in medication adherence and diastolic blood pressure than those receiving usual care. In people who were adherent at baseline (n = 241), TLC showed no significant difference in adherence between the two groups over the course of the trial.

Rudd 2004 used a nurse-led intervention to help improve adherence to hypertension medication. The intervention group (n = 74) received a call from a nurse at one week and one, two, and four months. These patients received baseline counseling on the use of an automated blood pressure device, advice on improving adherence to medication, and discussion of how to recognize drug side effects. The nurse also changed medication dosage if needed, and asked permission from the doctor if a new medication was introduced. This intervention led to positive results for adherence measured with eDEM pill caps in comparison to a group of patients receiving usual care (n = 76). This intervention also proved beneficial for the intervention group in significantly reducing both systolic and diastolic blood pressure, but the adjustment of medications by the interventions nurse may mean that this was due to increased medication rather than increased adherence.

Schroeder 2005 used a nurse-led adherence support group to help patients in the intervention group (n = 128) talk about concerns with the diagnosis of hypertension and problems they might have with their medication. The first session was 20 minutes long, and a 10 minute reinforcement session was held 2 months later. The control group (n = 117) received standard care for hypertension. Adherence was measured with MEMS pill bottle caps to calculate

'timing adherence', 'correct taking' adherence, and 'taking adherence'. Blood pressure was collected as a measure of clinical outcome. There were no statistically significant results for blood pressure or any measure of adherence, despite the large sample size.

MarquezContreras2005 reported positive findings for two interventions to help control hypertension and increase adherence to anti-hypertensive medication. The first intervention was a telephone intervention group (TIG) where patients received telephone calls to reinforce adherence from a nurse who asked participants specific questions about their medication and gave feedback on adherence performance. In the second intervention, patients received mailed communications (MIG) to promote adherence through education in hypertension and reinforcement of medication adherence. The control group (n = 212) received routine care. Percentage adherence via pill counts was shown to be significantly greater on all visits in both TIG (n = 216) and MIG (n = 212) than control. There were significant reductions in blood pressure in all groups but greatest improvements were seen in TIG. The TIG group also showed significantly better control of blood pressure at the end of the study in comparison to the control group.

A later study by Marquez Contreras and colleagues (MarquezContreras2006) incorporated an automatic blood pressure monitor for patients allocated to the intervention group (n = 100). Patients receiving the intervention also received cards to record their blood pressure measurements and instructions on how to use the monitor. A phone call was made to these patients to explain how to use the monitor and how frequently the measurements should be taken. Adherence to hypertension medication, measured with MEMS pill bottle caps, revealed a significantly greater rate in the intervention group than in the control group (n = 100). At 6 months there were no differences between the two groups for systolic and diastolic blood pressure.

A comprehensive pharmacy care program by Lee and colleagues (Lee 2006) showed promising results for adherence and some clinical outcomes in patients with both hypertension and hyperlipidemia. Patients assigned to the pharmacy care program (n = 83) received individualized medication education, their medication dispensed using blister packs to promote adherence, and a follow-up meeting every two months with a clinical pharmacist. The intervention was compared with a group of patients receiving usual care (n = 76) for treatment of hypertension and hyperlipidemia. A pill count showed significantly greater adherence rates for patients receiving the intervention. While there was no difference for low-density lipoprotein cholesterol and diastolic blood pressure levels between the two groups, intervention patients had significantly lower systolic blood pressure than the control group.

Diabetes mellitus

Six studies evaluated adherence interventions for patients with diabetes. Piette 2000 evaluated the effect of bi-weekly 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 significantly fewer problems with medication adherence. Patients in the intervention group also had lower glycosylated haemoglobin levels, lower serum glucose levels and fewer diabetic symptoms than those in the control group.

Wysocki 2001 reported 6- 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 (US$100) for attending all sessions. Although it was not evident immediately post-treatment, BFST was associated with an improvement in medication adherence at 6 and 12 months. However, BFST had no effect on 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.

In Yopp 2004 adolescent patients with type 1 diabetes were randomized to a multisystemic therapy (n = 27) or usual care (n = 26). Multisystemic therapy (MST) is a home-based psychotherapy administered by a multidisciplinary team to understand how the patient's poor metabolic control is related to other systems (i.e.: peers, school, families) and to determine how these factors affect their health status. The Diabetes Management Scale showed no difference between the intervention and control group for adherence to insulin. However, the 24-Hour Recall Interview showed significant results in favour of the intervention group for insulin use but not for glucose testing, diet, and exercise. Glycosylated haemoglobin levels were not significantly different between the two groups, however, glucose meter reading frequency increased in the intervention group.

Ellis 2005 also used MST on adolescent patients diagnosed with type 1 diabetes and randomized to receive the intervention (n = 64). Therapists met with families assigned to receive the intervention two to three times per week. These meetings ended when the treatment goals were met. MST interventions targeted problems with adherence to insulin the family, peer network, and the broader community in which the family was associated. The control group of patients (n = 63) received usual care for their diabetes treatment. Despite the intensive intervention, neither adherence nor clinical outcomes differed significantly between the two groups.

Odegard 2005 tested a pharmacist-led intervention to develop a diabetes care plan (DCP) for patients allocated to the intervention group (n = 43) in comparison to a group receiving standard care (n = 34). The pharmacist developed the DCP with patients; this

was then communicated to their physician via electronic medical records. Medication-related problems requiring intervention were identified as part of the DCP. The pharmacist maintained regular contact with the participants with in-person or telephone meetings. For measures of self-reported adherence, intervention recipients reported more difficulty in remembering to take prescribed medications (56% intervention versus 35% control) at baseline. Control patients also reported significantly better adherence than intervention patients throughout the intervention period. Although glycosylated haemoglobin levels in the intervention were not significantly different from the control group, there was a significant decrease in both groups at the 6 to 12 month interval. These results did not change after stratifying by glycosylated haemoglobin levels or self-reported adherence.

Howe 2005 compared two interventions to usual care to improve adherence to treatment for children with type 1 diabetes. In addition to usual care by a nurse and endocrinologist, patients allocated to the education (ED) intervention (n = 21) received a one-time educational session by the study coordinator to provide families with basic diabetes management skills. The second intervention included the educational session described as well as a telephone case-management (ED+TCM) intervention (n = 26), which consisted of telephone calls to parents and children (if over 13 years) to review blood sugar levels, meal planning, changing insulin dosage, and behaviour management skills. This was compared to a group of patients who received usual care (n = 28) from a nurse and endocrinologist. An adherence questionnaire, completed by physicians, showed patients in the ED + TCM groups had significantly improved by 24% over a 6-month period in comparison to the group receiving usual care. Glycosylated haemoglobin levels were not significantly different between groups. This may have been due to the small sample size.

Human immunodeficiency virus (HIV)

A number of investigations assessed interventions to enhance adherence to antiretroviral therapy for HIV. Knobel 1999 reported significant improvements in adherence to highly active antiretroviral therapy (HAART) and significant reduction of viral loads in patients receiving individualized counseling involving detailed information about drug therapy, adaptation of treatment regimens to suit the patient's lifestyle, phone support and monthly clinic visits.

In another study evaluating a psycho-educative intervention ("primarily to improve patients' knowledge and customs in handling medication to increase self-efficacy"), Tuldra 2000 assessed effects among HIV patients prescribed HAART. In an intention-to-treat (ITT) analysis, no improvements were found in adherence or clinical outcomes, although the P values bordered on the 0.05 significance level. A per protocol analysis showed improvements in adherence 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 might 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.

In Pradier 2003, patients in the intervention group received an educational and counseling approach based on the principles of motivational psychology, client-centered therapy and the use of an "empathic therapeutic to enhance participants' self efficacy". The intervention focused on cognitive (knowledge, beliefs, assumptions about medication), emotional (uncertainties, loss of hope, anxieties), social (stigma associated with the disease) and behavioral (plans to achieve treatment adherence) determinants affecting adherence and consisted of three individually delivered sessions by nurses lasting 45 to 60 minutes. Both self-reported adherence (available for 83% of patients) and mean difference in HIV RNA between baseline and six months (for all patients) were significantly improved in the intervention group, versus control. However, the clinical significance of these findings was unclear - the adherence rate was based on self-report in an unblinded trial, the mean HIV RNA (measuring viral load) was no different at six months for the two groups, and no actual clinical outcomes were reported.

The intervention in Berrien 2004 consisted of eight structured home visits over a three-month period by the same experienced home care registered nurse. The visits were designed to improve knowledge and understanding of HIV infection, to identify and resolve real and potential barriers to medication adherence, and ultimately to improve adherence. In the control group, clinicians and social workers provided standard medication adherence education at clinic appointments generally scheduled at three-month intervals. Medication adherence, as measured by pharmacy report of refill frequency, was substantially better in the intervention group than in the control group. The intervention group also showed improvement in self-reported adherence in comparison to the control group, although the difference was not quite statistically significant. Again, the small sample size (n = 20 for intervention group and n = 17 for control group) limits the power of the study. No statistical differences in CD4 T-cell counts or viral load were observed between groups.

The Tools for Health Empowerment (THE) course is an 11-module educational program for HIV-infected patients and their informal caregivers in which interactive small group sessions are facilitated by a healthcare professional trained in the principles of adult learning, with skills-building exercises aimed at behavior change in participants, flip charts, videotapes, patient logbooks, and patient workbooks. Rawlings and his colleagues (Rawlings 2003) only used four modules focusing on patient empowerment, HIV pathogenesis and treatment, and medication management and adherence. These were delivered to the intervention group (one session per week) during weeks one through four of this clin-

ical trial. No benefit was shown for patient adherence, virological suppression or immunologic changes.

Weber 2004 investigated whether cognitive behavior therapy could improve medication adherence. Participants were randomly assigned to a psychotherapist and given the contact information to schedule their own first appointment. Protocol defined a minimum of 3 and a maximum of 25 sessions within the one-year study period. The method of intervention had to be based on concepts of cognitive behavior therapy. Both intervention and control groups continued to receive standard care, including monthly visits for 12 months with assessments of clinical and laboratory data, course of treatment, drug adverse events and HIV-1 RNA. CD4 lymphocyte counts were measured every three months. Follow-up of participants continued with six monthly visits. There was no significant difference in mean adherence between the two groups, but both groups had very high mean adherence rates (92.8% versus 88.9%), and a significantly higher proportion of intervention group patients were at or above 95% adherence (70% versus 50%). The two groups did not differ for viral outcomes. Perhaps the standard care worked very well in this situation or the small sample size (n = 32 for intervention group and n = 28 for control group) reduced the power of the study to detect a difference in outcomes between the groups.

In Andrade 2005, patients were randomized to receive an individualized adherence counseling session each month (n = 29) or usual care (n = 29). Both groups received general education about the barriers to adherence, hazards of non-adherence, and discussions about their prescribed highly active antiretroviral therapy (HAART) regimen with a pharmacist each month. The intervention group also received a Disease Management Assistance System (DMAS) device that was programmed with reminder messages and dosing times for each medication in the HAART regimen for HIV patients. No significant difference was found for adherence measures between groups. However, when this data was stratified by memory-intact patients and memory-impaired patients, the memory-impaired patients in the intervention group showed significant improvement. For clinical outcomes, the intervention group showed a significant decrease in plasma HIV RNA viral load but no difference was found for CD4+ cell counts.

Collier 2005 used serial supportive calls from a nurse to HIV patients assigned to receive the intervention (n = 142). Telephone calls to patients were made approximately 1 to 3 days after the initiation of the study regimen and at weeks 1, 2, 3, 6, 12, and every 8 weeks thereafter, for a maximum of 16 telephone calls over the course the study. The control group comprised HIV patients receiving usual care (n = 140), consisting of in-person counseling by a nurse at the start of antiretroviral therapy and phone calls to patients if necessary. Adherence rates, measured with a questionnaire, and time to virologic failure were not significantly different between groups.

In Remien 2005, the intervention involved couples-focused therapy to increase adherence to antiretroviral therapy (ART) and subsequently improve clinical outcomes. The patients with HIV and their partner met with a nurse for four sessions over the course of five weeks. These sessions addressed treatment and adherence education, adherence barriers, communication and problem-solving strategies, and tips to optimize partner support. Adherence rates to ART, measured with MEMS pill bottle caps, were not significantly different between the intervention and control group at 32 weeks. HIV RNA viral load and CD4+ cell counts were also not significantly different between the two groups.

Samet and colleagues (Samet 2005) randomized patients to receive the ADHERE (Adherence to Drug for HIV, an Experimental Randomized Enhancement) intervention (n = 74) administered by a nurse or usual care (n = 77). The intervention had four components: a) assessment and discussion of the patient's alcohol and substance abuse; b) a medication timing device to improve adherence; c) enhancement of perceived efficacy of medications; and d) individualized HIV counseling. A one-hour session occurred at baseline, with shorter home visits occurring at 3 weeks, at 1 month, and 3 months after randomization. All baseline characteristics were approximately the same except the CD4 cell count, which was significantly higher in the intervention group at baseline. No significant differences were found for medication adherence at short-term and long-term follow-ups. CD4 cell counts and HIV RNA viral loads were also not significantly different between groups.

In Van Servellen 2005 a nurse practitioner provided modular instructions to patients randomized to the intervention (n = 43), which included five sessions aimed at increasing patients' HIV knowledge and abilities to communicate with medical staff. After the sessions, the nurse practitioner phoned or met with patients to address their risk for non-adherence. While a trend was present for intervention patients to report better adherence than control (n = 43), it did not reach significance. Using the criteria for greater than 90% adherence, the control group showed a decline in adherence at 6 weeks and 6 months. Patients in the intervention group showed an increase in the proportion reporting greater than 90% adherence at 6 weeks but not at 6 months. Using the criteria of greater than 95% adherence, the intervention group showed a trend towards being more adherent than the comparison group ($P > 0.10$). There were no significant differences between the two groups for HIV RNA viral loads, CD4+ cell counts, and disease progression.

Rheumatoid arthritis

Two studies tested adherence interventions for patients with rheumatoid arthritis. Brus 1998 evaluated an intervention involving six patient education meetings focusing on adherence with both medication therapy and a number of physical activities in patients with rheumatoid arthritis. Four two-hour meetings were offered during the first month of the intervention, and reinforce-

ment 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 (n = 29) did not demonstrate any improvement in adherence or clinical outcomes compared with patients in the control group (n = 31) who simply received a brochure on rheumatoid arthritis.

In Hill's study (Hill 2001) of rheumatoid arthritis, all patients in the education program (n = 51) were seen by a rheumatology nurse practitioner for a 30-minute appointment at monthly intervals over a 6-month period comprising seven visits. The non-education cohort group (n = 49) received the same D-penicillamine (DPA) drug information leaflet as the intervention group. This was in question-and-answer format and supplied information about DPA, how and when to take it, unwanted side effects, and safety monitoring. There was significant difference in adherence, but no difference in improvement of clinical outcomes at six months. The sample sizes of both Brus 1998 and Hill 2001 were small, so that the power to detect improvements in adherence or clinical outcomes was very low.

Dyslipidemia

Four studies concerned dyslipidemia. One study by Lee and colleagues (Lee 2006) is previously described with the hypertension studies as this study aimed to improve adherence to medication for patients with both hypertension and hyperlipidemia using a comprehensive pharmacy care programme. A pill count showed significantly greater adherence rates for patients receiving the intervention. While there were no differences for LDL-C and diastolic blood pressure levels between the two groups, intervention patients had significantly lower systolic blood pressure than the control group.

Peterson 2004 provided enhanced pharmacy support for patients in the intervention group (n = 45). A pharmacist educated the patients on the goals of lipid-lowering treatment and the importance of lifestyle issues in dyslipidemia and of adherence with therapy. The pharmacist assessed patients for drug-related problems, and measured total blood cholesterol levels using point-of-care testing at patients' homes monthly. Patients in the control group (n = 49) received standard medical care. There was no further contact with patients in the control group after the initial collection of baseline data, until six months had lapsed. This intervention did not improve self-reported adherence or reduce cholesterol levels between the two groups. The power of the study was limited by the small sample size.

MarquezContreras04a reported a significant difference in adherence and treatment outcome between two study groups. The control group of 63 patients received usual medical treatment, which included oral information about hypercholesterolemia and its control, brochures about dietary recommendations, 3 month-long prescriptions for a cholesterol-lowering medication, and titration of that medication if indicated at 3 months. The intervention group of 63 patients received this care, and also received a telephone call at 7 to 10 days, 2 months, and 4 months. The telephone intervention improved the percentage of patients complying with lipemia treatment according to pill counts, produced a larger mean decrease in total cholesterol and LDL-C over six months of treatment, and resulted in more patients reaching goals for their overall cholesterol profile and LDL-C.

Brown 1997a (details provided earlier) compared regular niacin with a polygel controlled-release formulation of niacin for lipid lowering. Adherence was significantly greater for the controlled-release preparation and a higher proportion of patients receiving it achieved the lipid control goal over eight months.

Mental health

Adherence studies for mental health disorders were methodologically challenging to interpret or accept at face value. Some interventions were highly complex and it was unlikely that their effects were mediated solely through changes in medication adherence. For example, Zhang and colleagues (Zhang 1994) demonstrated that there was an effect of family therapy that was independent of increased medication adherence in preventing relapses among patients with schizophrenia. This study might be confounded, and thus ineligible for our review, but the details of the interventions were not clearly enough described to determine if this was the case.

The generalizability 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 generalize the findings of these studies to settings in which either usual care was more vigorous, or the intensive intervention was not feasible. Strang 1981 allocated patients with schizophrenia to receive either family therapy or individual support sessions. There were fewer relapses for patients receiving family therapy than individual support sessions. The rate of adherence was also higher for those in family therapy. Xiong 1994 reported no significant difference between groups for adherence. However, significant clinical outcomes in favour of the intervention group were observed for rehospitalisation, number of days of rehospitalisation, months of employment and less psychopathology.

One study (Chaplin 1998) tested whether educating schizophrenic patients about benefits and adverse effects of their treatments, including tardive dyskinesia, decreases adherence with antipsychotic medications. Results showed no significant differences between study and control patients in terms of medication adherence or clinical deterioration. Again, with 28 patients per group in this study, the power to detect a difference in adherence or relapse was low. Five other studies, not about mental health (Al-Eidan 2002; Canto De Cetina 2001; Gani 2001; Howland 1990; Stevens

2002), also informed patients in intervention groups about the possible side effects of drugs without decreasing adherence, but this information was always part of more complex interventions that also included information about drug benefits and encouragement to adhere, except in the case of Howland.

O'Donnell 2003 also had 28 patients per group in their study to detect whether schizophrenic patients could benefit from "adherence therapy". The control group received non-specific counseling comprised of five sessions lasting 30 to 60 minutes. The experimental group received five sessions of "adherence therapy", each session lasting 30 to 60 minutes. The sessions covered a review of the patient's illness history, understanding of the illness and his or her ambivalence to treatment, maintenance medication and stigma. The results were not different for adherence or clinical outcomes, perhaps because both interventions were effective, or the power of the study was too low to detect a difference.

In an earlier study with a similar intervention, Kemp 1998 reported 18-month follow-up data on the effectiveness of "adherence 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. However, the follow-up rate was only 35% at 18 months. At 12 months, certain data were collected on more than 80% of patients. Patients receiving adherence therapy demonstrated significantly better social functioning and higher adherence ratings than those patients receiving non-specific counseling. However, there was no difference between the two groups for performance on the Brief Psychiatric Rating Scale. Only six-month data were available on insight, showing that patients who received adherence therapy had significantly greater insight into their condition and the effect of treatment than those receiving non-specific counseling.

Merinder 1999 was also unsuccessful in improving adherence or clinical outcomes. They found that an intervention consisting of family psycho-education (eight didactic interactive sessions) for 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 also of very small sample size (23 patients per group).

Razali 2000 compared the effects of "culturally modified family therapy" (CMFT) with "behavioral family therapy" (BFT) for patients with schizophrenia. Both interventions were delivered by a psychiatrist in a university hospital in West Malaysia. At six months and one year, patients in the intervention group (CMFT) had significantly higher adherence 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. However, this result did not take "clustering" into account: one psychiatrist treated all the control patients, while a second psychiatrist treated all the intervention patients. Further, it was possible that the therapist himself might be a factor in the outcomes reported in this study and thus must be considered part of the intervention and control procedure.

Ran 2003 was a second successful trial of enhancing adherence and clinical outcomes among patients with schizophrenia. The interventions in the family education group included:
a) Family education conducted once per month for nine months. During each visit, which lasted one and a half to three hours, patients' relatives were taught basic knowledge of mental diseases, treatment and rehabilitation. Advice and information were given according to the patient's specific condition, such as the stage of illness, recent onset or chronic. The patients were encouraged to join the meeting.
b) Multiple family workshops held once every three months. During the workshop, general questions were discussed, and relatives shared the experiences of caring for patients.
c) Crisis intervention conducted when necessary (e.g. for attempted suicide, aggressive and destructive behavior).
The local village broadcast network was also employed for health education during the first two months. There were two control groups. Patients in the drug treatment group (the first control group) only received drug prescriptions but no further support from the study team. In the second control group, patients were neither encouraged nor discouraged to take the medication, and they could seek assistance from other doctors in the local area if they wished. The psychoeducational intervention improved treatment adherence and decreased the rate of relapse compared with the two control groups. Other than the relapse rate, the intervention group did not improve clinical status compared with the drug treatment group, but both were better than the second control group.

One study evaluating educational interventions (Peveler 1999) compared the effects of treatment information leaflets, drug counseling 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 long, which is shorter than our usual 6 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. (Counseling about drug treatment, however, did result in significant improvements in adherence and clinical outcomes. Nonetheless, because the follow-up was less than six months in duration, the results for counseling are not considered in the conclusions of this review.)

Another complex intervention resulted in improvements in adherence and depression symptoms in Katon 2001. In this study, medication adherence and depressive symptoms were improved

through a program involving patient instruction (book and videotape), 2 visits to a depression specialist, 3 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), 4 personalized mailings at 2, 6, 10 and 12 months, and telephone follow-up assessments at 3, 6, 9 and 12 months. Patients in the intervention group had greater adherence to adequate dosage of 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.

Rickles 2005 randomized patients with depression to a Pharmacist-Guided Education and Monitoring (PGEM) program (n = 31) or usual care (n = 32). A pharmacist contacted patients 3 times within a 3-month period and patients were followed for 6 months from baseline. Some goals of this intervention were to assess patients' antidepressant knowledge, address concerns and treatment goals, to follow-up on patient non-adherence, and to help them better use their antidepressants. For follow-up calls, pharmacists used a monitoring tool to guide their follow-up on any issues or concerns identified in earlier calls. Intention-to-treat analysis showed no significant differences in missed doses (per protocol analysis revealed significantly lower percentage of missed doses for the intervention group at 6 months). The rate of missed doses at the end of the study period was significantly lower in the PGEM group than the control group. The number of depression symptoms, measured using the Beck Depression Inventory II, was not significantly different between the intervention and control groups.

Vergouwen 2005 randomized patients with depression to take part in a Depression Care Programme (DCP) (n = 81) by their general practitioners or usual care (n = 96). Participants in the DCP group received a newsletter about depression and adherence before scheduled visits with their practitioner. They also completed homework assignments to show their comprehension of this knowledge prior to each visit. Adherence rates were not significantly different between the two groups at 26 weeks. Although the Beck Depression Inventory showed a decrease in depressive symptoms in both groups by week 10, this trend was not statistically significantly different at week 26 between groups. The Clinical Global Impression and Symptom Checklist-90-Revised (SCL-90-R) also did not reveal differences between the two groups.

Heart failure

Sadik 2005 randomized patients with heart failure to usual care (n = 112) or to a structured care program (n = 109) led by a pharmacist. The intervention involved: simplification of drug therapy if appropriate, informational booklet about heart failure, and instruction on a self-monitoring programme (signs and symptoms of heart failure and adherence to prescribed medication). Self-reported medication adherence was shown to be significantly improved after 12 months in the intervention group compared with the control group. Clinical outcomes such as pulse, blood pressure, 2-minute walk test, symptoms of heart failure, forced vital capacity, and quality of life were shown to be significant at the P = 0.05 level, but it should be noted that patients were not blinded to study group, most measures were subjective, and, while there were more hospital admissions in the control group, the intervention group had more casualty department visits.

Ischemic heart disease

Coull 2004 investigated senior lay health mentoring in older people with ischemic heart disease. The intervention group participated in a mentor-led group, with monthly two-hour long meetings in community facilities over a one-year period. The core activities covered in the program were lifestyle risk factors of smoking, diet and exercise; blood pressure and cholesterol; understanding of and ability to cope with ischemic heart disease; and drug adherence. Input was provided from a pharmacist, cardiac rehabilitation specialist nurse, dietician, welfare benefits advisor and Recreation Services. Volunteer lay health mentors, aged 54 to74 years and recruited from the local community, led the groups. Both intervention and control groups continued to receive standard care. The mentored group reported significantly more adherence with medication (measured by self-report) than the control group but there was no improvement in the treatment outcome. In this study setting, the patients' medications could not be standardized, and they used a self-reported method to measure adherence.

Oral anticoagulant therapy

Laporte 2003 assessed the adherence with, and the stability of, oral anticoagulant therapy following an educational intervention that began prior to hospital discharge. While in hospital, the standard education group received the minimum information consistent with ethical oral anticoagulant therapy with no particular emphasis on the necessity of strict adherence. Patients in the intensive education group received information through visual material about the causes of anticoagulation instability and the importance of strict adherence, were visited daily in hospital by nurses and physicians to repeat some items, and were tested daily about their knowledge. Either standard or intensive education was given until hospital discharge. The results for adherence and treatment outcome were not significantly different between the groups at a follow-up period of three months. Both the standard education group and the intensive education group had high adherence; thus, standard education appeared to be sufficient in this situation.

Tuberculosis

Walley 2001 tested the effectiveness of directly observed treatments (DOTS) for new, sputum-positive tuberculosis. One hundred and seventy patients were assigned to DOTS with direct observation of treatment taking by health workers 6 days per week; 165 patients were assigned to DOTS with direct observation of treatment by family members; and 162 patients were assigned to self-administered treatment, obtained by visiting a health facil-

ity once every two weeks. There was no additional benefit in the treatment adherence or clinical cure of tuberculosis from direct observation of treatment over and above usual service, whether supervision was by health workers or family members.

Contraception

Canto De Cetina 2001 determined the effect of pretreatment counseling on discontinuation of 150 mg depot-medroxyprogesterone acetate (Depo-Provera, DMPA) given for contraception. The women in the counseling group received structured pretreatment counseling with indications about the mode of action of DMPA and the common side effects of the drug, including the possibility of irregular menstrual periods, heavy bleeding, spotting, and amenorrhea. To mentally prepare users for potential side effects, it was stressed that these side effects would be not detrimental to their health. Although the structured counseling group had a statistically significantly lower dropout rate than the routine counseling group, there was no difference in the number of pregnancies. In this situation, however, longer follow-up (greater than 12 months) would be needed to observe an effect on the incidence of pregnancy.

Complex regimens in the elderly

Nazareth 2001 and Volume 2001 investigated the effectiveness of a pre-discharge pharmacy intervention for elderly hospitalised patients on multiple medications, compared with usual care. Neither study found a benefit. In Nazareth 2001, patients in the intervention group, who were aged 75 years and older and on four or more medicines, were visited by community pharmacists at home between 7 and 14 days after hospital discharge. The pharmacists assessed the patient's understanding of, and adherence to, their medication regimens and intervened when appropriate. Interventions included counseling patients or carers on the purpose and appropriate doses of the medication, disposing of excess medicines and liaising with general practitioners. The pharmacists arranged further community visits at their discretion. Patients randomized to the control group were discharged from hospital following standard procedures. These included a discharge letter to the general practitioner indicating the diagnosis, investigations and current medications. There were no significant differences between the groups in adherence or the proportion of patients re-admitted to hospital. In Volume 2001, patients in the intervention group, aged 65 years old, and using three or more medications, received a comprehensive pharmaceutical care service. Pharmacists met with patients for 30 to 45 minutes to better understand their drug-related needs, acquiring data through the Pharmacists' Management of Drug-Related Problems (PMDRP) form, and then provided frequent follow-up communication with the patient and other caregivers, documenting all contacts in a standardized format. Control pharmacies provided usual services, with pharmacist-patient contact being triggered by receipt of a prescription (the different services between intervention and control pharmacies were reported in Kassam 2001). No difference in adherence or clinical outcome was observed over the year of the study.

DISCUSSION

The current version of our review updated our 2005 version (Haynes 2005) with 21 new studies (Andrade 2005; Bailey 1999; Beaucage 2006; Collier 2005; Ellis 2005; Hederos 2005; Howe 2005; Lee 2006; MarquezContreras2005; MarquezContreras2006; Odegard 2005; Portsmouth 2005; Remien 2005; Rickles 2005; Rudd 2004; Sadik 2005; Samet 2005; Schroeder 2005; Van Servellen 2005; Vergouwen 2005; Yopp 2004). The interventions and findings of these studies did not substantively alter the conclusions of the previous version of the review. Of these 21 studies (evaluating 22 interventions), 8 interventions were associated with significant improvements in at least 1 adherence measure at 6 to 12 months. Six of the studies demonstrated improvements in at least one clinical outcome at six to nine months. It should be noted that the clinical improvements in both older and newer studies were seldom in major clinical outcomes such as death or stroke; rather, the studies usually evaluated intermediate outcomes such as serum cholesterol, diastolic blood pressure, or CD4+ cell count.

Overall, for short-term treatments, four of ten interventions reported in nine RCTs showed an effect on both adherence and at least one clinical outcome, while one intervention reported in one RCT significantly improved patient adherence, but did not enhance the clinical outcome. For long-term treatments, 36 of 81 interventions reported in 69 RCTs were associated with improvements in adherence, but only 25 interventions led to improvement in at least one treatment outcome. 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, counseling, family therapy, psychological therapy, crisis intervention, manual telephone follow-up, and supportive care. The diversity, complexity, and uncertain effects of the interventions make generalizations problematic about which interventions work and which do not. Even the most effective interventions did not lead to large improvements in adherence and treatment outcomes.

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. There were very few improvements to potentially promising interventions and there was only one innovative intervention to improve adherence in this update of the review. One study investigated whether increasing social support for patients with HIV by using a couple-based therapy would have

an effect on adherence to antiretroviral therapy (Remien 2005). Remien and colleagues found no significant benefit with respect to adherence or clinical effects. Compared with the many thousands of trials for individual drugs and treatments, only a few relatively rigorous trials of adherence interventions exist. These provide little evidence that medication adherence can be improved consistently, within the resources usually available in clinical settings, and that this will predictably lead 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 labor-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 might have underestimated intervention effects. In this 2007 update, about half of the studies used measures of adherence that are imprecise, often relying on self-report, a method that is known to overestimate adherence (Gordis 1979; Haynes 1980; Stephenson 1993) and that could easily blur any differences between groups. However, more studies (43%) are incorporating objective measures of adherence such as using Medication Event Monitoring System (MEMS) pill bottle caps. These caps contain a microchip that measures the date and time at which the bottles are opened. Other objective measures that were used include pharmacy refill records. In our view, this is a productive and necessary step forward in the field of adherence research, as it will lead to further valid and reliable results. Although objective measures are more expensive, they provide a more accurate measure of true adherence and should be incorporated into studies whenever possible.

Further, some interventions might work well, but they were not tested well. For example, once or twice a day dosing might secure higher adherence than three or four times a day. However a study looking into dosing frequency only compared once versus twice a day, finding a difference in adherence but not in clinical effects (Baird 1984). Portsmouth 2005 changed the dosing regimen for one drug from twice-daily to once-daily for HIV patients. No benefit was shown for adherence or clinical effects. Given that HIV patients take many prescribed medications, changing the dose for one drug might not be enough to improve adherence. 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 probably did not represent those in usual care well.

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 shows that only 36 of the 78 investigations to date have met this standard, so most studies lack 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 study reporting no improvement in either adherence 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 was clearly low powered. In a more recent example, group meetings were shown to improve adherence to asthma medication on some measures (Hederos 2005) but failed to show an improvement in any of clinical measures. There were less than 35 patients per group, making the study underpowered. Of the 21 newly identified studies for this review, 40% suffered from low power due to small sample size, including Andrade 2005, Hederos 2005, Howe 2005, Odegard 2005, Portsmouth 2005, Rickles 2005, Van Servellen 2005, and Yopp 2004.

Of the 21 new RCTs in this update describing 24 interventions to improve adherence to prescribed medications, only 5 studies (21% of the new studies) showed positive outcomes for both adherence and clinical outcomes (Lee 2006; MarquezContreras2005; MarquezContreras2006; Rudd 2004; Sadik 2005). (This is not statistically different than the 18 of 58 interventions (31%) reported in the last update of this review (Haynes 2005). The medical condition of the population and the complexity of interventions vary greatly in these five studies but one commonality is that there were more than 75 patients per group, which indicates adequate power to detect a meaningful difference. Three of these studies involved allied health professionals such as nurses and pharmacists leading the adherence interventions. Generally, the interventions included in this review were led by research teams and multidisciplinary teams, which cannot easily be translated into real-life practice. If the roles of nurses and pharmacists can be expanded to include counseling with patients intended to enhance medication adherence, this may be feasible in practice. As such, the effectiveness of adherence interventions led by allied health professionals should be further explored.

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 showed that adherence with appointments for medical care could 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, that 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 (Simpson 2006), 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. However, there were no measurable benefits even from the combined interventions.

It is interesting to note that a recent but unpublished manuscript for a meta-review—a review of systematic reviews on interventions designed to improve medication adherence—demonstrated findings that were not consistent with the results of this review (Sahota 2007). The meta-review was performed with the objective of integrating current research on patient adherence interventions, to uncover and suggest promising interventions warranting more extensive investigation. All the included reviews examined interventions intended to improve adherence with prescription medicine and the results were drawn from the primary articles that each review investigated. Complex strategies were shown not to be the most effective in the meta-review, rather, it was some of the more simple interventions that displayed the best results in improving adherence: the simplification of dosage regimen (12/15 primary studies (80%) statistically supported the intervention) and the use of adherence enhancing packaging (10/13 primary studies (77%) statistically supported the intervention). Moreover, a recent meta-analysis performed by Bangalore and colleagues (Bangalore 2007) supports the effectiveness of interventions that simplify dose regimens for patients. They demonstrated that fixed-dose combinations, designed to simplify the medication regimen, decreased the risk of non-adherence by 24 to 26% in comparison to free-drug combination regimens, lending support—limited, since the results are based only on nine studies—for dosage simplification as an effective strategy to improve adherence. van Dulmen 2007 also recently published a meta-review of 38 adherence reviews published between 1990 and 2005, and reported positive findings in 23 of 38 reviews, including support for "mechanical interventions" such as modified dosage regimens. It is important to note, however, that none of these meta-reviews required the measurement of clinical outcomes. Thus, the reviews reported only adherence results and included studies that measured only adherence, as well as studies that measured both adherence and clinical endpoints. This may contribute to the differences in the conclusions of this review and other reviews and meta-reviews in the area. As stated before, improving medication adherence will not necessarily translate into clinical benefits for the patient and so both measures need to be taken in account. Hence, interventions that have been shown to be successful in improving adherence outcomes, such as dosage simplification, need to measure clinical outcomes as well to further validate their effectiveness.

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 generalizability to usual practice settings. This also raised 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. Furthermore, some studies (e.g. MarquezContreras2005) reported that the patients in control group received "standard medical care", but did not describe what the standard medical care included. If the standard medical care took adherence factors into account, whether explicitly or inherently, it might have worked very well. If so, the result could be no significant difference between the control group and the intervention group, not because neither intervention worked but because both did.

To determine applicability to patient care, we only selected studies that measured both adherence and treatment outcome. However, the measures for both were not often objective and, when subjective, the assessors were sometimes aware of the study group of patients, increasing the possibility of biased assessments.

No studies examined major clinical endpoints. For chronic dis-

eases, the follow-up was relatively short-term, 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 (e.g. 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 refer to issues of adherence. Reviews with a major focus on adherence include Harvey 2001 on obesity; Volmink 2007 on tuberculosis; Gibson 2002 on asthma; Schroeder 2004 on hypertension in ambulatory settings; Heneghan 2006 on long-term medications; Orton 2005 on malaria; Rueda 2006 on HIV; Lancaster 2002, Lumley 2004, Silagy 2004 and many others on smoking. Also, van Dulmen 2007 is a recent a meta-review indicating the focus, scope and conclusions of 38 reviews of adherence to medical treatment.

AUTHORS' CONCLUSIONS

Implications for practice

For short-term treatments, several interventions improve adherence, including simply informing patients that all of the prescribed medication is to be consumed, but these findings were not consistent from study to study, with only 4 of 10 trials reporting benefits for both adherence and clinical outcomes. The studies were typically small, however, and may have hidden real benefits. For long-term treatments, simplifying the dosage regimen and several complex strategies, including combinations of more thorough patient instructions and counseling, reminders, close follow-up, supervised self-monitoring, rewards for success, family therapy, couple-focused therapy, psychological therapy, crisis intervention, and manual telephone follow-up can improve adherence and treatment outcomes. If there is a common thread to these at all, it is more frequent interaction with patients with attention to adherence. However, these complex strategies for improving adherence with long-term medication prescriptions are not very effective despite the amount of effort and resources they can consume.

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 fuller 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.

There are many factors that can contribute to non-adherence such as: frequent changes to drug regimen, misunderstanding prescribing instructions, limited education about the medication, and forgetfulness (Vlasnik 2005). In our view, important innovations are more likely to occur if investigators join across clinical disciplines to tackle the problem, and take into account the resistance that many patients have to taking medicines (Pound 2005), perhaps including patients in the development of new interventions. There is little evidence that low adherence with medications is disease- or regimen-specific, with the possible exception of psychiatric disorders (Haynes 1979b).

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 (Weinberger 2002) had only 1113 patients and none of the trials sought effects on major morbidity or mortality. Most studies had fewer than 50 patients per group. 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. Interventions involving allied health professionals appear to be promising and should be examined further for their effectiveness for adherence and clinical benefit.

If complex interventions show positive effects, it would be appropriate to test their components in factorial studies.

Future studies on improving adherence to prescribed medication should incorporate more objective measures for adherence to provide a more accurate view of the intervention's effect.

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 1987a).

POTENTIAL CONFLICT OF INTEREST

None known.

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** Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	Al-Eidan 2002
Methods	Patients were randomly assigned to the intervention or control group using a sealed envelope technique.
Participants	Seventy-six dyspeptic patients, who at endoscopy were found to have gastritis, duodenitis or ulceration, and a positive Helicobacter pylori (H-pylori) urease test, were recruited. Patients were excluded if they were unsuitable for eradication therapy or hypersensitive to its ingredients.
Interventions	After diagnosis and enrollment, all patients were to be prescribed a 1 week regimen of lansoprazole 30 mg daily, amoxicillin 1 g twice a day (bid), and clarithromycin 500 mg bid. Patients in the intervention group received their medication from the hospital pharmacy and were counseled by the hospital pharmacist (average 9.5 minutes) on: their disease and the importance of eradication of the organism; the medicines to be taken and possible side-effects, the importance of compliance with the prescribed dosage. Intervention patients received a patient information leaflet about their medication and the need for H-pylori eradication. They were also given a compliance diary chart and telephoned 3 days after the initiation of therapy to provide further counseling about the importance of complying to the medication regimen. Control patients were treated according to normal hospital procedures. They were given a letter to be given to their GP with the recommendation to start triple-therapy and a letter explaining the nature of infection, the need for treatment

	and the importance of compliance (ambiguous in the article, but it seems that the latter letter went to the patient rather than (just) their doctor).
Outcomes	Compliance Measurements 1) Patient interview by telephone (structured questionnaire) by the same pharmacist for both groups, after the intended end of the eradication course 2) Pill counts on returned medication when patients returned for a urea breath test. Patient clinical outcome measures included: -H-pylori status: Assessed with a urea breath test 4 to 6 weeks post eradication therapy. Eradication was defined as an absence of H-pylori. -Adverse Effects: Contacted by hospital pharmacist 10 days post endoscopy and asked about any adverse effects experienced from the eradication therapy. -Modified version of the Gastrointestinal Symptom Rating Scale: to assess the presence and severity of dyseptic symptoms. The presence and severity symptoms was judged by the patient. They were assessed at the time of endoscopy, at 1-month and 6-months.
Notes	
Allocation concealment	A – Adequate

Study	**Andrade 2005**
Methods	Sixty-four patients were randomized in this study with 32 in the intervention group and 32 in the control group. Allocation concealment and method of randomization were not described.
Participants	Enrolled patients who were 18 years of age or older, able to self-medicate, and currently receiving care at the Johns Hopkins Moore (HIV) Clinic. Subjects eligible for inclusion were either previously treatment naive and initiating highly active antiretroviral therapy (HAART) for the first time or antiretroviral experienced and switching HAART regimens. Among subjects in the latter group, we included only those who had received 3 or less HAART regimens before study enrollment. Exclusion criteria were inability to self-medicate, presence of severe dementia, and institutionalization.
Interventions	All subjects participated in an individualized, 30 minute adherence counseling session each month and received adherence feedback from a standardized transcript that provided general education about the barriers to adherence, the hazards of non-adherence, and their prescribed HAART regimen. A clinical pharmacist with extensive experience in the field of Human Immunodeficiency Virus / Acquired Immunodeficiency Syndrome (HIV/AIDS) provided adherence counseling and feedback. Patients in the intervention group were also given the Disease Management Assistance System (DMAS) device for 24 weeks. The DMAS device was programmed with reminder messages and dosing times for each medication in the HAART regimen. Devices were inspected monthly and reprogrammed when the HAART regimen was changed or replaced if they were lost or malfunctioning. Patients in the control group did not receive the DMAS.
Outcomes	Adherence was assessed monthly with the DMAS, data from the electronic drug-exposure monitoring (eDEM) caps and completion of the AIDS Clinical Trials Group (ACTG) Baseline Adherence Questionnaire during the initial study visit and the ACTG Follow-up Adherence Questionnaire during subsequent visits. Four-day average adherence was calculated as the number of prescribed doses minus the number of missed doses, divided by the number of prescribed doses. For the DMAS device, adherence was calculated as the number of times the response button was pressed divided by the number of medication prompts during the 4-day period preceding the study visit. Clinical endpoints included CD4+ cell count and plasma HIV RNA load were assessed at baseline and at weeks 12 and 24 of follow-up. Validated neuropsychological (NP) tests were used to assess attention, memory, new learning, psychomotor speed, and executive functions and administered twice during the study, at baseline and after 24 weeks of HAART. Symptoms of depression were assessed using the Center for Epidemiologic Studies Depression (CES-D) scale. Patients were also questioned about active illicit drug use and alcohol use during the past 4 days.
Notes	The DMAS prompting device improved adherence for memory-impaired subjects but not for memory-intact subjects; this was shown at 24 weeks with a 20% increase in adherence for the memory-impaired group compared with 6% for the memory-intact patients. Although the DMAS resulted in improved adherence, the overall mean adherence score was only 77% for DMAS users with memory deficits. This is lower than the optimal adherence rate of 95% required for optimal viral suppression.
Allocation concealment	B – Unclear

Characteristics of included studies (*Continued*)

Study	**Ansah 2001**
Methods	If children coming in on Monday received pre-packed tablets, those who came in on Tuesday received syrup. The formulation assigned to a particular day changed from week to week. 155 received pre-packed chloroquine tablets, and 146 received syrup.
Participants	Children aged 0 to 5 years diagnosed with malaria at the clinic over a 6-week period received either pre-packed tablets or syrup by random assignment (n = 301).
Interventions	Chloroquine tablets were dispensed in polythene packages divided into three parts each containing the daily dose. The brand of tablets used for this study easily dissolved in water to form a homogenous suspension. Caregivers were advised at the dispensary to crush the tablets and to add a little honey or sugar to the mixture to mask its bitter taste. Staff of the health centres pre-packed the chloroquine on a weekly basis. Packages were available for eight treatment regimes based on weight. The other group got chloroquin syrup.
Outcomes	The measure used to dispense the medication (in the case of syrups), frequency and duration of administration. A standard graded measuring syringe was used to assess the volume of the implement used for measuring the dose at home, and then compared adherence to treatment and its cost between the two groups.
Notes	The investigators varied which day of the week was assigned to which intervention, making this trial closer in methodology to a cluster randomized trial.
Allocation concealment	D – Not used

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 healthcare outcomes: Four status scales were employed in assessing healthcare 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 – Unclear

Characteristics of included studies (*Continued*)

Study	Bailey 1999
Methods	Patients (n = 236) were stratified by asthma severity (moderate or severe) and randomly assigned to the 3 groups using the closed-envelope technique: University of Alabama at Birmingham (UAB) Asthma Self Management group (n = 78), UAB Core-Elements group (n = 76) and usual care group (n = 78). As well, standard computer procedures were employed to create a stratified, blocked randomization schedule, which consisted of block sizes of six to ensure two out of every six patients in each stratum were assigned to each group. Immediately following randomization, staff collected baseline data and implemented the designated educational treatment.
Participants	All subjects were patients in the clinics of the UAB Division of Pulmonary and Critical Care Medicine with a primary diagnosis of asthma who met the following diagnostic criteria: (1) recurrent episodes of dyspnea or wheezing, (2) objective evidence of significantly increased resistance to airflow during episodes, (3) objective evidence of improvement in airflow when symptom-free, and (4) moderate to severe (rather than mild) asthma as assessed by their asthma care physician. New and current patients were included in the study, although patients who had participated in the earlier self-management study were excluded.
Interventions	UAB Asthma Self Management Program (n = 78): The core component of the UAB Asthma Self Management Program (ASMP) was a skill-oriented self-help workbook, which patients were counseled about in a one-on-one session and during two asthma support group meetings. The workbook included information on physiology of asthma, asthma medications, identification and avoidance of triggers, detection of and response to asthma attacks, and asthma care services. The 1-hour counseling session included reviewing the workbook content and skills, identifying personal expectations, asthma triggers, and barriers to adherence, and practicing inhaler use until patients were able to do so correctly. Patients were also given peak flow meters and trained to use them for early detection of impending asthma attacks. Asthma support groups, facilitated by a health educator, consisted of 4 to 6 patients with asthma and, if possible, asthma control partners (spouses or close friends). Support group meetings were held once each month many patients came every month. Patients were encouraged to share asthma concerns, discuss adherence problems, and exchange patient-initiated solutions. Patients received 2 telephone calls and a follow-up letter at 1, 2, and 4 weeks, after the counseling session. The first telephone call allowed the discussion of problems and to collect baseline peak flow readings and to help determine their expected peak flow rates. The letter reinforced actions to take at different levels of peak flow readings. The second telephone call provided closure for the intervention. Overall, the intervention spanned about 6 to 8 weeks for patients. UAB Core-Elements Program (n = 76): This program consisted of a revised, shortened workbook that was given to patients. It was reviewed in a brief (15 to 20 minutes) one-to-one counseling session. Patients were trained to use inhalers and peak flow meters and rehearsed until these devices were used correctly. A follow-up telephone counseling session was conducted approximately one week later to review the patient's medication regimen and inhaler and peak flow meter skills. Two weeks later, a follow-up letter was sent to patients, stressing the importance of adhering to the prescribed regimen and responding immediately to a drop in peak flow rate or other early signs of an attack. Usual-care control group (n = 78): Patients received the education that was the standard practice of their physician. They also received a standardized set of pamphlets that contained information about asthma. No steps were taken to ensure that patients read the pamphlets, and no special counseling, support groups, or telephone calls were provided.
Outcomes	Compliance was measured using two 4-item self-reports, which were based on the prototype self-report scale described by Morisky et al (25) but were modified to be more applicable to asthma. The psychometric characteristics of the asthma therapy adherence scales were good to excellent. Adherence was analyzed in terms of the percentage of subjects with the highest possible scores on these scales. Four clinical outcome measures addressed asthma status, specifically, the impact of asthma on respiratory symptoms and illnesses, functional status, and use of healthcare services. Two scales addressed the severity of asthma symptoms in the past 7 days and the number of respiratory illnesses in the past 3 months. The functional impairment scale assessed the extent to which asthma had a negative impact on daily activities in the past 3 months. The scale for measurement of use of healthcare services classified patients as users if they had visited an emergency department for asthma and/or been hospitalized for asthma in the past 6 months. Other patients were classifies as nonusers. These measures also analyzed the percentage of subjects who obtained the highest possible score as users.

Notes	
Allocation concealment	C – Inadequate

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 to 250 mg) daily, or propranolol 160 mg (range 120 to 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 to 0900 hours), and in the evening (12 hours later), or (2) Betaloc Durules 200 mg every morning (0600 to 0900 hours).
Outcomes	Two measurements of adherence were utilised: (1) tablet counts at 6 and 10 weeks, and (2) spot checks of metoprolol concentration in the urine at 6 and 10 weeks. The mean heart rate, systolic and diastolic blood pressures were assessed before, during, and after the trial, and compared between the two treatment regimens.
Notes	Outcome assessments were not blinded to study group.
Allocation concealment	B – Unclear

Study	**Beaucage 2006**
Methods	Patients (n = 255) were randomly assigned to (1) Pharmacist telephone follow-up intervention (PTFI; n = 126) or (2) usual pharmacist intervention (UPI; n = 129). Randomization was stratified by pharmacy in balanced blocks of 10 patients (1:1 ratio) using a computer-generated random-number table and provided to the pharmacist investigators in sealed envelopes identified by patient number. Patients were randomized sequentially by patient number.
Participants	Patients had an expected duration of antibiotic treatment of 5 to 14 days, spoke French or English, were able to converse over the telephone, and were available for a telephone call during and at the expected end of antibiotic treatment and for up to 48 hours thereafter. Patients were excluded from the trial if they were initiating prophylactic antibiotic treatment, were not self-managing their medication, were already participating in a clinical trial, in the opinion of the pharmacist, required intense clinical follow-up, or would benefit from more intensive follow-up in a special medical hospital clinic.
Interventions	Pharmacist telephone follow-up intervention (PTFI) patients received a telephone call from a pharmacist on day 3 of their antibiotic treatment. The pharmacist documented the patient's general condition, checked for adverse effects and the patient's understanding of the dosage, stressed the importance of adherence to treatment, and offered encouragement. Patients were invited to ask questions and to contact their pharmacist if needed. At the initial pharmacy visit, Usual Pharmacist Intervention (UPI) patients were invited to contact their pharmacist if needed. They received no telephone calls during their treatment.
Outcomes	Compliance was measured by patients reporting the number of antibiotic tablets or capsules left. Compliance was defined as the percentage of tablets consumed of the total number of tablets provided. Patients receiving azithromycin treatment and those who had a change in antibiotics during their treatment were excluded from this analysis. The clinical outcomes of patients were measured by asking for the number of infectious symptoms and their descriptions; as well, a 5-point Likert scale was used to evaluate the severity of the infections. This was measured at baseline and upon completion of the treatment.
Notes	
Allocation concealment	A – Adequate

Study	**Becker 1986**
Methods	Random allocation without an indication of concealment.

Characteristics of included studies (*Continued*)

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 – Unclear

Study	**Berrien 2004**
Methods	37 patients were randomized 1:1 to either the home intervention or control group using the Small Table of Random Digits. The randomization process was number-based, with patient names not identified. The randomization list was held by the clinical coordinator of the HIV program and kept in a locked file.
Participants	All eligible HIV-positive patients (n = 37) followed in the program. Informed consent was obtained from each participant's legal guardian. Children ranged in age between 1.5 to 12 years of age (mean 8.7 years) for the intervention group and 5 to 11 years (mean 8.4 years) in the control group. Assent was obtained from all minors older than 7 years of age.
Interventions	The intervention group received eight structured home visits over a 3-month period by the same home care experienced registered nurse. The visits were designed to improve knowledge and understanding of HIV infection, to identify and resolve real and potential barriers to medication adherence, and ultimately to improve adherence. Spanish-speaking case managers, incentives, notebooks with stickers and pill-swallowing training were also part of the home visit training sessions. In the clinic setting for control group, the physician, nurse and social worker provided standard medication adherence education at clinic appointments generally scheduled at 3-month intervals. Phone follow-ups and a single home visit were planned if the staff felt they were needed. Visual aids for remembering medications, medication boxes, beepers, and general technical and emotional support were regularly offered. The clinic nurse contacted the family by telephone when the patient was starting a new medication, was having difficulty with adherence, or needed clarification and support. A single home visit was planned when and if the clinic staff believed medication adherence was poor despite the implementation of the above listed techniques.
Outcomes	Knowledge and adherence were measured at the beginning of the study and at the end of the intervention. Changes in viral load and CD4 counts were measured at baseline and after treatment, or for 6 to 11 months beyond the initial study period.
Notes	
Allocation concealment	A – Adequate

Characteristics of included studies (*Continued*)

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 (four times each day (qid)) versus polygel controlled release niacin (twice-daily dosage (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), low-density lipoprotein (LDL), and high-density lipoprotein (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.
Notes	
Allocation concealment	B – Unclear

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 rheumatoid arthritis (RA), based on 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. Disease-modifying anti-rheumatic drug (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 to 78) and number of swollen joints (0 to 52). The DAS ranges from 0 to 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 – Unclear

Study	**Canto De Cetina 2001**
Methods	After the initial injection (Depo-Provera), 350 patients were randomised to receive either structured counseling or routine indications about the contraceptive method (175 women in counseling group and 175 women in control group).
Participants	The study was conducted at the Family Planning Clinic of the "Centro de Investigaciones Hideyo Noguchi" in Merida, Yucatan, Mexico. Women were eligible if they were between the ages of 18 and 35 years old and living in a rural area. They had to have proven fertility, have regular menstrual cycles during the previous 6 months, not breastfeeding, and have at least one child. They also had to have normal PAP smears of grade CI, CII, and be willing to use Depot Medroxyprogesterone Acetate (DMPA) as the only contraceptive agent during the course of the study and be willing to return to the clinic every 3 months. Exclusion criteria included current or a history of thrombophlebitis, thromboembolic disorders, hypertension, cerebral vascular disease, active or chronic liver disease, known or suspected breast or genital organ malignancy, endocrinopathy undiagnosed, vaginal bleeding, and diabetes mellitus. 350 women voluntarily participated in this study.
Interventions	The initial injection (Depo-Provera) was given within the first 5 days of the menstrual cycle. The women in the first group (counseling group) received a structured pretreatment counseling with indications about the mode of action of DMPA, the common side effects of the drug, including the possibility of irregular menstrual periods, heavy bleeding, spotting, and amenorrhea. To mentally prepare users for potential side effects, it was stressed that these side effects would be not detrimental to their health. These indications were repeated at each follow-up visit. Women were encouraged to return to the clinic if they had concerns about the effect that DMPA was having on their health; the information was provided by means of an audiovisual set specially developed to uniform messages on risks, benefits and overall characteristics of the injectable contraceptive Patients of the second group (control group) were simply told that they were in the study to investigate the efficacy of an injectable contraceptive, and they were given routine information on the expected side effects of DMPA.
Outcomes	Women of both groups were evaluated in the clinic and had gynecological examinations. They were instructed to fill out the diary cards.
Notes	The pregnancy rates were not measured. Injectable DMPA is used in order to prevent pregnancy. The author might have been referring to the compliant rates of the two groups as an indicator or clinical health.
Allocation concealment	B – Unclear

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 (TD). 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 medication they were considered non-compliant.
Notes	In this study, the 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 – Unclear

Study	**Colcher 1972**
Methods	Random allocation without an indication of concealment.
Participants	All children (aged 1 to 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	There was no indication of blinding of the outcome measures.
Allocation concealment	B – Unclear

Study	**Collier 2005**
Methods	Patients (n = 282) were randomized upon entry to receive either each study site's usual adherence support measures (n = 140) or each study site's usual adherence support measures and scripted serial telephone calls from study site staff members (n = 142). Exact method of allocation concealment was not described.

Characteristics of included studies (*Continued*)

Participants	Patients had < or = to 200 CD4+ T cells/mm3 or >80,000 HIV RNA copies/mL of plasma at screening, no or limited previous antiretroviral therapy (no previous use of lamivudine, nonnucleoside reverse transcriptase inhibitors, or protease inhibitors), hemoglobin > or = to 9.1 g/dL (for men) or > or = to 8.9 g/dL (for women), > or = to 850 neutrophils/mm3, > 65,000 platelets/mm3, hepatic aminotransferase levels < 5 times the upper limit of reference values, and amylase levels < 1.5 times the upper limit of reference values, and could not be pregnant or breast-feeding.
Interventions	The intervention group received serial, supportive telephone calls. Study site staff members (mostly nurses) followed a standardized script for telephone calls and received training by the study team. Spanish and Italian translations of the English script were provided. The telephone calls focused on each subject's medication-taking behavior, and study site staff members identified barriers to adherence and developed individualized strategies to increase adherence. During the telephone calls, the study site staff members also provided social support and assistance with the management of side effects. The telephone calls were to be made at specific times: 1 to 3 days after the initiation of the study regimen and at weeks 1, 2, 3, 6, 12, and every 8 weeks thereafter, as long as the subject continued to receive the assigned study regimen, for a maximum of 16 telephone calls over the course of 96 weeks. For each telephone call, a minimum of two attempts were made to contact the patient before leaving a counseling or general message. Also, a complete telephone call was one where all the topics described above were discussed, however, if that didn't occur, calls were categorized as being only partially completed. The usual adherence support measures included an average of 35 minutes of in-person counseling provided by a study site nurse or pharmacist at the start of treatment. According to a study site survey, 67% of study sites reported providing written materials to study subjects as part of their usual adherence support measures. As well, 41% reported making at least 1 telephone call to selected subjects (deemed at being high risk for low adherence) as part of their usual support measures; however, the telephone calls were made to a minority of patients, the number of calls per patient was limited, and the content was not standardized.
Outcomes	Compliance was measured at baseline using a standardized adherence questionnaire and a follow-up questionnaire evaluating medication-taking behavior during the preceding 4 days at weeks 8, 16, 24, 48, 72, and 96. The primary health outcome was a measure of antiretroviral drug activity, specifically, the time to virologic failure. Virologic failure was defined as (1) having > than or = to 200 HIV RNA copies/mL of plasma at or after week 24 or (2) having an increase of > 1.0 log10 above nadir levels or an increase to or above baseline levels before week 24 or (3) having 2 consecutive HIV RNA levels > than or = to 200 copies/mL at any time after having 2 consecutive HIV RNA levels < 200 copies/mL.
Notes	
Allocation concealment	B – Unclear

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 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 – Unclear

Study	**Cote 2001**
Methods	All patients were stratified for treatment center. The first 45 patients among 126 patients were recruited in the control group to avoid contamination. Subsequent eligible patients were randomized in the two educated groups. Only the randomized groups are eligible for our review.
Participants	126 patients were enrolled in the study, but 105 attended for randomization. Patients (aged > 18 years) with an acute exacerbation of asthma who had not previously taken part in any asthma educational program. Patients older than 40 years of age in whom the best forced expiratory volume in 1 s (FEV1) was lower than 80% of predicted were excluded. All patients with concurrent medical illnesses that in the judgment of the investigators contraindicated study participation were also excluded.
Interventions	The patients in Group C (control) received the usual treatment given for an acute asthma exacerbation. In addition to standard treatment as for Group C treatment, patients in Group Limited Education (LE) were given a self-action plan that was explained by the on call physician. The action plan used "traffic lights" (green, yellow, red) to describe specific states of asthma control based on Peak Expiratory Flow and symptoms and actions that the patient should take for each state (pages 1415 to 1416). Subjects were all instructed by a respiratory therapist or study nurse in the proper use of an inhaler. In addition to what patients in Group LE received, the patients in Group Structured Education participated in a structured asthma educational program based on the PRECEDE model of health education within 2 weeks after their randomization. Structured educational intervention group Group SE. In addition to what patients in Group LE received, the patients in Group SE participated in a structured asthma educational program based on the PRECEDE model of health education within two weeks after their randomization. Briefly, this model takes into consideration three different issues that are important when dealing with health-related behaviors: predisposing factors (belief, attitude, knowledge); enabling factors (community resource, family support); and reinforcement. The teaching was provided individually or in small groups according to patient preference. The intervention focused mainly on self-management. To increase patient self-confidence in making his or her own treatment decisions, the interaction with the patient was based on the self-efficacy theory of Bandura. Reinforcement was provided at the 6-month follow-up visit.
Outcomes	Compliance with inhaled corticosteroids was evaluated according to the patient's own estimation at 2 weeks and 12 months. Patient outcome measures included number of urgent visits for an acute exacerbation of asthma, lung function tests, knowledge, use of an action plan, compliance with inhaled corticosteroids, quality of life score.

Notes	The method of measuring adherence is very insensitive because it only indicates whether the person had a prescription for inhaled corticosteriods, not whether they used it.
Allocation concealment	B – Unclear

Study	**Coull 2004**
Methods	319 patients were randomized by the researchers after giving informed consent. 165 patients were in the mentoring group and 154 in the control group. Eligible patients were stratified by sex, disease modality (myocardial infarction or angina) and location (five areas identified).
Participants	Patients aged 60 or over that had been either admitted to hospital, or had attended the outpatient department, with a clinical diagnosis of ischaemic heart disease (IHD). Exclusion criteria were terminal illness, an abbreviated mental health test score < 8, inability to complete 3 minutes of Bruce Protocol exercise tolerance testing, awaiting angioplasty or coronary artery bypass grafting, participation in another clinical study involving coronary risk factor modification or at the request of their consultant or general practitioner.
Interventions	Intervention consisted of participation in a mentor-led group, through attending monthly 2-hour-long meetings in community facilities over a 1-year period. There was an average of 10 patients per group, each led by two mentors. Both intervention and control groups continued to receive standard care. The core activities covered in the programme were lifestyle risk factors of smoking, diet and exercise; blood pressure and cholesterol; understanding of and ability to cope with IHD; and drug concordance. Each mentored group was also encouraged to develop its own agenda. Input was provided from a pharmacist, cardiac rehabilitation specialist nurse, dietician, welfare benefits advisor and Recreation Services. Volunteer lay health mentors, aged 54 to 74 recruited from the local community, led the groups.
Outcomes	Perceived change in taking of medication was measured using a five point Likert scale in the exit questionnaire. Outcome measures were changes in blood pressure, cholesterol and medication, and cardiovascular events; non-medical support requirement, health status and psychological functioning, and social inclusion.
Notes	This is self-reported concordance and there was no attempt to standardize the regimens, so this may be explained by differences in medications, insensitive/biased measure of adherence, or low power.
Allocation concealment	D – Not used

Study	**Ellis 2005**
Methods	Randomization was completed immediately after baseline data collection by the project statistician. To ensure equivalence across treatment condition, randomization was stratified by level of glycosylated hemoglobin levels (HbA1c) at the baseline visit. A total of 127 adolescents and their families were randomized to either receive the multisystemic therapy (MST) intervention group (n = 64) or the control group (n = 63).
Participants	Patients were 1) diagnosed with type 1 diabetes for at least 1 year; 2) had an average HbA1c [A1C] > or = to 8% during the year before study entry, as well as a most recent A1C > or = to 8%; 3) aged 10 to 17 years, and 4) sufficient mastery of English to communicate with therapists and complete study measures. Patients were excluded from the study if they possessed moderate/severe mental retardation or psychosis.
Interventions	Adolescents assigned to the intervention condition received multisystemtic therapy (MST) plus standard medical care. MST is an intensive, family-centered, community-based treatment. Therapists conducted a multisystemic assessment of the strengths and weaknesses of the family, then tailored treatment goals and interventions to each family to best treat the adherence problem. MST interventions targeted adherence-related problems within the family system, peer network, and the broader community systems within which the family was embedded. The therapists drew upon evidence-based intervention techniques that included cognitive behavioral therapy, parent training, and behavioral family systems therapy; the various interventions were incorporated at home, school, with peers, and within the healthcare system. Therapists were expected to meet with families a minimum of two to three times per week at the beginning of treatment. Treatment was terminated when treatment goals were met and the mean length of treatment in the study was 5.7 months. Adolescents in the control condition received standard medical care. Standard care at the hospital

	where adolescents were cared for consisted of quarterly medical visits with a multidisciplinary medical team composed of an endocrinologist, nurse, dietitian, social worker, and psychologist.
Outcomes	Patients completed the Twenty-Four Hour Recall Interview to assess adherence behaviors for the previous day. Clinical outcomes included HbA1c values, number of ER visits and number of hospitalizations.
Notes	
Allocation concealment	B – Unclear

Study	**Farber 2004**
Methods	Randomization was accomplished using a randomized block design in which block size was randomly allocated between 2 and 4 to ensure that the size of the intervention and control groups was equivalent. Randomization was not balanced on any other variables. Random group assignments were generated and were placed in sequentially numbered envelopes. Envelopes were not opened to reveal group assignments until informed consent was obtained and enrollment (baseline) interviews were completed.
Participants	56 subjects to be included in the study, subjects were between the ages of 2 to 18 years, had State of Louisiana Medicaid insurance, had a telephone at home, had a history of asthma, had not been intubated or mechanically ventilated for asthma, did not have other clinically significant (i.e., moderate to severe) chronic illness, presented to the ED when an investigator was available, had informed consent provided by a parent or guardian, child voluntarily assents to participation in the study if older than 12 years.
Interventions	Subjects in the intervention group received basic asthma education; instructions on use of a metered-dose inhaler with holding chamber; a written asthma self-management plan illustrated by zones colored green, yellow, and red; a sample age-appropriate holding chamber; and prescriptions for medication needed to implement the plan. This medication included an inhaled corticosteroid drug for everyday use and a quick-acting bronchodilator for use as needed. The importance of seeking urgent medical care in the red zone was emphasized. Three brief followup phone calls were placed to patients in the intervention group at 1 to 2 weeks, 4 to 6 weeks and 3 months after enrollment.
Outcomes	Self-reported method to measure the compliance plus pharmacy refills. Medicaid claims files used to assess frequency of medication dispensing, dates of asthma-related hospital admissions and dates of ED visits (identified by ICD-9) discharge diagnosis)
Notes	
Allocation concealment	A – Adequate

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 mm Hg or a diastolic blood pressure greater than or equal to 90 mm Hg 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

	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 – Unclear

Study	**Gallefoss 1999**
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. (Study reported in two papers).
Participants	Eligible subjects were patients with bronchial asthma or chronic obstructive pulmonary disease (COPD) between 18 and 70 years of age, not suffering from any serious disease such as unstable coronary heart disease, heart failure, serious hypertension, diabetes mellitus, or 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 participants were followed by their GPs and the intervention group received an education program and were then also transferred to a 1 year follow-up by their GPs. The educational intervention consisted of a specially-constructed 19-page patient 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. There were also two 2-hour group sessions (separate groups for asthmatics and patients with COPD) of five to eight people on two separate days. The COPD group received more information about tobacco weaning, but besides this the educational interventions were comparable. 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-minute individual sessions were then supplied by a nurse, and another one or two 40-minute individual 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 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 weeks of peak flow monitoring. The personal understanding of the treatment plan with regard to changes in PEF and symptoms was discussed and tested.
Outcomes	One paper reported compliance of regular medication, calculated as a % age: (dispensed Defined Daily Dosage/ Prescribed Defined Daily Dosage) x 100 during the 1-year 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. The other paper reported that four simple health-related quality of life (HRQoL) questions were asked at baseline. HRQoL as measured by the St-George's Respiratory Questionnaire (SGRQ) at 12 months plus the same 4 questions asked at baseline. FEV measured via spirometry prior to randomization and at 12 months.
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 – Unclear

Study	**Gani 2001**
Methods	101 patients were randomized into three groups: A (n = 30) with drug therapy alone, B (n = 35) with drug therapy plus training on the use of nasal spray, and C (n = 36) the same as B plus a lesson on rhinitis and asthma. All patients received mometasone furoate nasal spray for 8 weeks as regular therapy, plus rescue medications on demand. Symptoms and drug consumption were evaluated during the pollen season.
Participants	One hundred and one patients (62 male, 39 female, age range 12 ± 60 years) had suffered for at least 2 years from Seasonal Asthma and Rhinitis (SAR) solely due to pollens (grasses, birch, Parietaria, and Compositae), Patients with sensitization to multiple pollens were included, whereas sensitization to cat dander, mites, or mold was a reason for exclusion. Exclusion criteria were as follows: anatomical abnormalities of the upper respiratory airways (septal deviation, polyposis), previous or ongoing immunotherapy, pregnancy/ lactation, chronic treatment with systemic corticosteroids, malignancies, and major psychiatric disorders.
Interventions	The first group of patients (group A = 30 patients) was given only the drug with the instructions provided by the manufacturer. The second group (group B = 35 patients) received a brief training on how to use the nasal spray and were given simplified written instructions on the use of the device. The third group (group C = 36 patients) also attended a 1-hour informal lesson on the clinical and pathogenic aspects of SAR, the treatment strategy, the correct use of medications, and the possible side-effects of drugs. A trained allergist (one per clinic) gave the lesson to patients, and the set of slides used was the same in the three clinics.
Outcomes	All patients completed a symptom diary, recording the presence and severity of their symptoms (self-reported). The compliance with therapy was evaluated on the basis of the returned diaries and canisters. Symptoms were subdivided as follows: nasal (itching, sneezing, rhinorrhea, and blockage), ocular (itching, redness, lacrimation, and swelling), and respiratory (cough, wheezing, and chest tightness). The severity of symptoms was graded on a 10-cm visual analog scale (0: no symptoms, 10: severe symptoms). Patients were also required to record carefully each dose of each drug taken, in addition to the nasal corticosteroid.
Notes	8 week-follow-up during the whole pollen season is satisfactory for the seasonal disease.
Allocation concealment	B – Unclear

Study	**Ginde 2003**
Methods	RCT: Consenting patients were randomized to the ED (intervention) or pharmacy (control) group.
Participants	The study was conducted from November 2001 to May 2002. During the 6-month study period, all adult patients (> 18 years old) presenting to the ED for whom an outpatient prescription for a macrolide antibiotic was being considered in discharge planning were eligible for the study. The need for outpatient treatment with an antibiotic was determined by the attending Emergency Physician who was primarily responsible for the patient. Patients who were unwilling or unable to give informed consent or were unavailable for telephone follow-up were excluded from the study. In addition, all females of childbearing potential were given urine pregnancy tests, and pregnant or breast-feeding females were excluded. 77 patients were recruited.
Interventions	Patients in the ED group were provided a full course of azithromycin (6 x 250 mg) at no charge and given instructions on the proper dose and frequency before discharge from the ED. Patients in the pharmacy group received a written prescription for a full course of azithromycin before discharge from the ED. To minimize the potential for economic bias, the patients were able to fill their prescriptions free of charge at a 24-hour pharmacy located 8 blocks from the hospital.
Outcomes	The primary outcome was compliance of obtaining medication as determined by pharmacy records. A secondary outcome was compliance in completing the course of medication as determined by a telephone survey. Measurement of Clinical Health Outcomes: Return visits to the ED and hospitalization.
Notes	The prescription filling rate for the control group is based on the assumption that control patients used a participating pharmacy eight blocks away that provided the drug free of charge and patients were apparently not asked if they filled their prescription elsewhere. The prescription filling rates could have been clarified for the control group. The "course completed" rate is based on self-report on a telephone call and there was

	no indication that interviewers were blinded to group or if the exact question given. Technically, this study qualified for the review, but the reliability and credibility of these measures is suspect. This intervention may be impractical in any setting where giving drugs out for free is not possible.
Allocation concealment	B – Unclear

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 to 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 (eg. 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 non-steroidal anti-inflammatory drugs, 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 medication electronic monitoring system (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 blood pressure (BP) readings were trough values. Two readings were taken after 10 minutes 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	
Allocation concealment	B – Unclear

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 – Adequate

Study	**Hederos 2005**
Methods	The parents of the 60 children were randomized consecutively in groups of four to either the intervention or the control group by the nurses. This resulted in 32 children in the intervention group and 28 children in the control group. The three doctors that were involved in the group sessions also performed the follow-up visits. Blinding could not be completed since the intervention was led by their physicians.
Participants	Patients were 60 children aged between 3 months to 6 years and had been given a diagnosis of asthma in the region, 1 to 2 months earlier. Asthma was defined by three or more episodes of wheezing before 2 years of age, or the first wheezing episode after the age of 2, or the first episode of wheezing in a child with other atopic diseases. The patients also had fulfilled the following criteria implying high risk for permanent asthma: wheezing without symptoms of upper respiratory tract infection (URTI) and/or proven allergy and/or atopic heredity.
Interventions	The intervention consisted of meetings in a group setting with the parents. The sessions took place in the afternoon and lasted about 1.5 hours. Shortly after the children were diagnosed as an asthmatic, three meetings (one every week for three weeks) took place and a follow-up meeting took place 6 months later. Three paediatricians, three nurses and two psychologists were involved in these sessions: one nurse was present on all occasions, and the doctors and psychologists on three each. The goal of all the meetings was to reach the parents' "main worry" and, apart from teaching about asthma, the following key question was asked: "What is asthma to you?" The use of dialogue and peer education, whereby the group was encouraged to share personal experiences was emphasized. The control group, as well as the intervention group, received basic education about asthma and its treatment, including how to use the Nebunette, and information on environmental control at the first visit to the clinic. They received a written treatment plan where the principle was high dose (0.2 mgr4 of budesonide for 3 days) initially and then, in association with URTI, stepping down the therapy to the lowest possible dose according to the status of the child. The treatment was stopped if the child had no asthma for 6 months.
Outcomes	Compliance was measured in the following ways: 1) parents and doctors estimated adherence on a visual analogue scale (VAS) at inclusion, at 6 months and after 18 months; 2) adherence was measured between the 12- and 18-months follow-up visits using a diary in which the parents recorded the consumption of medicines, asthma symptoms and other illnesses; 3) all the Metered Dose Inhalers (MDIs) with budesonide used during this period were weighed and the real consumption was estimated; and 4) the adherence according to parents was calculated as the number of doses given according to the diaries/the number of doses prescribed * 100. The verified adherence was defined as the real number of doses/the number of doses prescribed * 100. The verified adherence was considered acceptable if the index was 50 to 150 and poor if the index was < 50. The following clinical outcomes were assessed: 1) parents estimated their children's asthma problems during the last 6 months, after 6 months and after 18 months on another VAS.; 2) three doctors classified the children according to GINA guidelines including medication in four groups: mild, moderate, rather severe and severe at inclusion, after 6 mo and after 18 months; 3) during the first 6 and last 6 months of the 18-month-long study, the parents noted how many days the child was hospitalized and how many times they had to seek emergency help due to asthma; and 4) frequency of exacerbations, defined by the need for parents to stay at home to take care of their child due to asthma symptoms.
Notes	

Allocation concealment	B – Unclear

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 twice a day., amoxycillin 500 mg three times a day., and metronidazole 400 mg three times a day, 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 two 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 healthcare 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. 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 – Unclear

Study	**Hill 2001**
Methods	Patients were stratified into bands of low, medium, or high knowledge of their rheumatoid arthritis (RA) by means of a validated patient knowledge questionnaire. 21 Patients in each band were randomly allocated to the Education Group and Control Group using a separate computer generated code for each band. This was done to ensure that the two groups had comparable levels of initial knowledge. Allocation was carried out by a clerk who had no study input or patient contact.
Participants	Rheumatologists referred 100 patients with active RA; all were deemed to require D-penicillamine (DPA) as their slow acting antirheumatic drugs (SAARD). Entry criteria required that all patients were aged 18 years or above, had a positive diagnosis of RA using the American Rheumatism Association criteria, a plasma viscosity (PV) > 1.75 mPa.s or a C reactive protein (CRP) > 10 mg/l. In addition, they should have two out of three clinical features: an articular index > 15, morning stiffness > 45 minutes, a minimum of moderate levels of pain. Patients were excluded if they had received DPA previously, had a contraindication such as kidney impairment or pregnancy, or were receiving incompatible concomitant drugs. Patients who were awaiting hospital admission were excluded as the nursing staff often give drugs during their stay.
Interventions	The chosen intervention was a Patient Education programme taught by a rheumatology nurse practitioner. Where practicable, variables that could confound the results were eliminated. All patients took the same

	SAARD, were given the same number and length of appointments, and were seen by the same rheumatology nurse practitioner. All patients were seen by the rheumatology nurse practitioner for a 30 minute appointment at monthly intervals over a six month period comprising seven visits. The Education Group received a comprehensive programme of Patient education based on the theory of self efficacy: a person's confidence in their ability to perform a specific task or achieve a certain objective. The non-education cohort received the same DPA drug information leaflet as the intervention group. This was in question and answer format and supplied information about DPA, how and when to take it, unwanted side effects, and described safety monitoring.
Outcomes	Clinical Health Outcomes included: PV, CRP, Three clinical assessments- Articular index (AI), Morning stiffness, Pain score.
Notes	
Allocation concealment	A – Adequate

Study	**Howe 2005**
Methods	A randomization schedule was produced using Statistical Analysis System (SAS) program with subjects blocked by race, age group, sex, and family structure (single versus two parents). Within each block, patients (n = 89) were randomly assigned to one of the three treatment groups: the standard care (SC) group (n = 28), the education (ED) group (n = 21) or the education and telephone case management (ED + TCM) group (n = 26). The group allocation for the remaining fourteen patients (not included in the study analysis) was not described.
Participants	Patients had two consecutive glycosylated haemoglobin (HbA1c) results of 8.5% or higher, were aged 1 to 16 years, and had been diagnosed with Type 1 diabetes for at least 1 year.
Interventions	Patients in the SC group received standard care from a nurse practitioner and endocrinologist, typically every quarter. During the 30-minute office visits, HbA1c value was obtained, blood glucose records were reviewed, problems were identified, target goals were determined, and education was provided as needed. Patients in the ED group received the standard care in the clinic. They also participated in a one-time education session with the study coordinator, a nurse, with the goal of providing families with basic diabetes management skills such as insulin administration and carbohydrate counting. Children older than 8 years were asked to participate in the education sessions. Families were given customized written guidelines including insulin doses for hyperglycemia and for varying carbohydrate loads. At the completion of the program, parents were expected to identify problems and to know when to call their nurse practitioner for assistance in insulin dose adjustment, for sick-day management, or for advice in coordination of the diabetes regimen. Patients in the ED + TCM group received both the standard care in clinic and the education program described above. They also received weekly telephone calls for 3 months or until the first clinic visit and then bimonthly calls for 3 months from the study coordinator. At the time of enrollment, subjects were given an appointment 3 months after the start of study. For children younger than 13 years, telephone calls were between the study coordinator and a designated parent. Some teens did elect to be involved in telephone calls as well. The study coordinator talked with both the teen and parent to ascertain that plans were clear between child and parent. The study coordinator followed a standardized telephone protocol to review blood sugars, safety issues related to hypoglycemia and hyperglycemia, problem-solving skills, diet and meal planning, and changing insulin dose. The study coordinator also discussed parenting and behavior management skills with parents as needed. Telephone calls were typically 5 to 15 minutes
Outcomes	The ADH (an adherence questionnaire) was used to evaluate child/family behaviors related to diabetes safety and control. ADH was obtained at baseline and at the end of study. The HbA1c values were used as clinical measures and their levels were obtained at baseline, at 3 to 6 months, and at end of study.
Notes	
Allocation concealment	B – Unclear

Characteristics of included studies (*Continued*)

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 was measured using the following methods: the mean number of erythromycin pills taken per day, patients reporting that they missed at least one pill, and the mean number of pills taken out of 40 pills.
Allocation concealment	B – Unclear

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 to 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 – Unclear

Study	**Katon 2001**
Methods	Patients were randomized to the relapse prevention intervention versus 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.
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 Symptom Checklist 20 (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 the Group Health Cooperative of Puget Sound (GHC) within the next 12 months, currently seeing a psychiatrist, limited command of English, or recently using lithium or antipsychotic medication.

Characteristics of included studies (*Continued*)

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 Healthcare 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 to 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 – Unclear

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. Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (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. 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 – Adequate

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 – Adequate

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/8h), zidovudine (300 mg/12h), and lamivudine (150 mg/12h). They included all patients with HIV infection receiving prescription for this combination of agents from July 1996 to December 1997.
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 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 – Unclear

Characteristics of included studies (*Continued*)

Study	**Laporte 2003**
Methods	A 2 by 2 factorial design with patients randomly allocated to warfarin (long half-life) or acenocoumarol (short-half life) and to either intensive education or standard education. Allocation concealment was achieved by central computerized randomization balanced in blocks of 2, 4 and 6 patients.
Participants	Patients over 18 years old were enrolled if they needed at least 3-month oral anticoagulant therapy (OAT) following IV infusion for a thromboembolic disease. Patients were excluded if they were pregnant, had any contra-indication to anticoagulant therapy, recent surgery (< 4 days) or progressive bleeding.
Interventions	Patients assigned to warfarin received a dose of 6 mg (up to 70 years old) or 4 mg (over 70 years) those assigned to acenocoumarol received a dose of 4 mg (up to 70 years old) or 3 mg (over 70 years). Subsequent doses were adjusted to maintain the international normalized ratio (INR) within the target range of 2 to 3. Patients took a single dose of the oral anticoagulant (OA) daily at 8pm. The standard education group received the minimum information consistent with ethical OAT with no particular emphasis on the necessity of strict compliance. Patients in the intensive education group received information about the causes of anticoagulation instability and the importance of strict adherence. The intensive education group were provided information through visual material, were visited daily by nurses and physicians to repeat some items, and were tested daily about their education. The education, either standard or intensive was given until hospital discharge.
Outcomes	The number of tablets left in the bottle were recorded at follow-up at 1, 2 and 3 months. Measurement of Clinical Health Outcomes: Lab INR measurements were made in the morning and recorded in the patient's diary. The raw INR levels, the % of INRs in target range, the % of time in target range and %age of dose adjustments were recorded. Follow up visits were scheduled at 1, 2 and 3 months. During each visit patients were asked about their symptoms or bleeding events.
Notes	The follow-up period was only 3-months but since the results proved to be negative it still meets the criteria for inclusion in the review.
Allocation concealment	A – Adequate

Study	**Lee 2006**
Methods	Patients (n = 159) were randomized to either usual care (n = 76) or continued pharmacy care (n = 83) in a 1:1 ratio using a computer-generated random number sequence. Patients were randomized in blocks based on the level of baseline medication adherence (above or below 55% baseline adherence). Neither the participants nor the clinical pharmacists assessing the outcomes were blind to the study group assignment.
Participants	Patients were from the Walter Reed Army Medical Center and were elderly men and women (> 65 years) taking 4 or more chronic medications daily. Patients were excluded from the study if they did not live independently or in the presence of any serious medical condition for which 1-year survival was expected to be unlikely.
Interventions	The intervention entailed a comprehensive pharmacy care program that consisted of 3 elements, including individualized medication education (using standardized scripts), medications dispensed using an adherence aid (blister packs) and regular follow-up with clinical pharmacists every 2 months. All medications were provided to patients in customized blister packs filled by pharmacy technicians and checked by clinical pharmacists. Patients were instructed to tape any medications not taken back into the blister pack, to account for any selective adherence. Usual care was defined as returning to their baseline (pre-study) status of medication provision; however, medication education and blister-packed medications were not provided. For the usual care group in phase 2, all medications were provided in new pill bottles with a 90-day supply and 1 refill prescription.
Outcomes	Compliance for the randomized stage was measured by the persistence of mean medication adherence. The clinical endpoints of the randomized stage were the changes in BP and LDL-C at study month 14.
Notes	
Allocation concealment	A – Adequate

Characteristics of included studies (*Continued*)

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 to 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 chronic obstructive pulmonary disease were excluded.
Interventions	The intervention group was invited to attend a 1 hour 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 peak expiratory flow (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. Quality of life was also assessed using the St. George's Respiratory Questionnaire (SGRQ), and patients use of medical services was assessed.
Notes	
Allocation concealment	A – Adequate

Study	**MarquezContreras04a**
Methods	A controlled, randomized clinical trial was conducted in 6 primary care centers in Huelva province of Spain.
Participants	126 people diagnosed with hypercholesterolaemia according to Spanish Consensus criteria were chosen: 63 in Control Group and 63 in Intervention Group. Recruitment took place from January to June 2001.
Interventions	The Control Group (CG) of 63 patients, who received the doctor's normal treatment, which included oral information about hypercholesterolemia, advice about its control, brochures about dietary recommendations, 3 month-long prescriptions for a cholesterol-lowering medication, and titration of that medication if indicated at 3 months. The Intervention Group (IG) of 63 patients received this care, and in addition, received a telephone call at 7 to 10 days, 2 months, and 4 months. The goal of the intervention was to establish the level of compliance, categorize this as adequate or inadequate, and make recommendations based on that. Level of compliance was determined by comparing the number of pills consumed to the number that should have been consumed (calculated using self-reported information about the number of pills remaining, number of pills dispensed, and fill date of the prescription). Compliance was defined as taking 80 to 110% of the pills that should have been taken thus far. Compliant patients were congratulated and encouraged to continue their good level of compliance as it would lower their risk of heart disease. Noncompliant patients were notified their behavior was considered noncompliant and encouraged to better comply with therapy as it would lower their risk of heart disease.
Outcomes	Pills were counted in person at 3 and 6 month follow-up visits to estimate compliance over the previous 3 months. Cholesterol, triglycerides, HDL-C and LDL-C were measured at the start, and at the third and sixth months.

Characteristics of included studies (*Continued*)

Notes	
Allocation concealment	A – Adequate

Study	**MarquezContreras2005**
Methods	Patients (n = 636) were randomly allocated to receive one of the two interventions, the telephone intervention (n = 216) or the mail intervention (n = 212), or usual care (n = 212). Allocation concealment was not specified.
Participants	Patients were eligible for participation in the trial if the following criteria were met: (i) Outpatients of either sex and between 18 and 80 years of age; (ii) newly diagnosed or uncontrolled phase I and II hypertension (JNC-VI criteria) requiring antihypertensive treatment; (iii) provision of patient informed consent in writing. Patients were excluded if they met any of the following criteria: (i) Patients who at the start of the study required two or more antihypertensive drugs for hypertension control; (ii) acute myocardial infarction; (iii) secondary hypertension; (iv) known side-effects and contraindications to the use of angiotensin AT1 inhibitors; (v) pregnant or breastfeeding women; (vi) patients with conditions capable of interfering with the study; (vii) patients planning to donate blood; (viii) participants in other research studies; (ix) patients cohabiting with another person taking the same antihypertensive medication. Study withdrawal criteria were as follows: (i) Inadequate therapeutic effect requiring an increase of more than 20% in the scheduled number of visits; (ii) patient decision not to continue with the study and/or schedule follow-up visits; (iii) concomitant illnesses or adverse effects that in investigator opinion, the patient needs be withdrawn from the study.
Interventions	Participants allocated to the telephone intervention group (TIG) received a controlled intervention in the form of three telephone calls: the first 15 days after the inclusion visit; the second and third being one week after visits 3 and 4. The telephone intervention was made by two expert nurses in this type of interventions. During the calls to patients in this group, the patients were reminded of scheduled visits and asked about the name, dosage and timing of their antihypertensive medication, and the number of remaining tablets. Patients were informed, according to the number of tablets in their possession, if they were good or poor compliance. In the event of good compliance, the patients were congratulated and encouraged to continue adhering to therapy. In the event of noncompliance, the patients were encouraged to comply, and the associated benefits were explained. For participants who were allocated to the mail intervention group (MIG), they received three mailed communications at home: the first 15 days after the inclusion visits; the second and third, being one week after visits 3 and 4; in order to promote compliance through health education in hypertension, reinforce compliance, and remind the subjects of the scheduled visits. The mailed messages included information about the following hypertension aspects: what is hypertension?; diagnosis of hypertension; symptoms; related risk factors; why is necessary to treat the hypertension?; what is the hypertension treatment?; and information about the correct taking of medication. Patients who were allocated to the control group (CG) received the center's routine primary care intervention and did not receive any additional intervention to improve adherence.
Outcomes	Compliance was assessed using a pill count. Percentage compliance (PC) was calculated from the following formula: PC = (Total no. of presumably consumed tablets/ total no. that should have been consumed)*100. Compliance was accepted if it was in the range of 80 to 110%. The study final PC for each patient was defined as the cumulative PC at the end of follow-up (at the end of the last visit or at the time of withdrawal), while the monthly PC was taken to be the PC recorded between one follow-up visit and the next. Blood pressure was measured as the clinical endpoint during the scheduled visits by the primary care physician. The final blood pressure reading was taken as the mean of the two measurements made.
Notes	
Allocation concealment	B – Unclear

Study	**MarquezContreras2006**
Methods	The patients (n = 250) were randomly assigned to one of the two groups, stratified by age and sex: a control group (CG) and an intervention group (IG). The randomization process was centralized and blind, performed using random number tables and by a person not involved in the follow-up.

Characteristics of included studies (*Continued*)

Participants	Patients were ambulatory patients between 18 and 80 years of age, newly diagnosed hypertensive patients or those already on antihypertensive treatment but not controlled and who did not have an electronic monitor for home blood pressure measurement (HBPM), patients with phase I or II arterial hypertension (AHT) according to the JNC-VI criteria, and patients who had given their written consent. Patients were excluded from the study if they were requiring two or more antihypertensive drugs at the start of the study, secondary AHT, pregnant or breast-feeding women, patients with diseases that could interfere with the study, patients who intended to donate blood, patients who were unable to give their consent, patients participating in other studies, and patients co-habiting with other individuals taking the same antihypertensive medication.
Interventions	Patients in this intervention, apart from receiving the usual care, also received an OMRON automatic monitor for home blood pressure measurement (HBPM). The patients received a kit in their home containing the monitor, an instruction manual, a summary of the functions, and a card on which to note the measurements. They were advised to follow the HBPM programme, which consisted of measuring the BP 3 days a week (Tuesdays, Thursdays and Saturdays), twice before breakfast (0800 to 1000 hours) and twice before supper (2000 to 2200 hours) and record these results on the card (four times a day). The patients received a phone call to explain how to use the monitor and follow the HBPM programme. The control intervention involved patients receiving the care usually provided by their general practitioners.
Outcomes	Compliance was measured using Medication Event Monitoring System (MEMS) and the percentage compliance (PC) was calculated by dividing the total number of tablets the patients were assumed to have taken by the total number of tablets that the patients should have taken and multiplying by 100 to obtain a percentage. Compliance was considered to be present in patients with a percentage compliance between 80 and 100%. Blood pressure (taken as the mean of two measurements) was the clinical outcome used.
Notes	
Allocation concealment	A – Adequate

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 to 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 operational criteria checklist for psychotic and affective illness (OPCRIT) 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.
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 – Unclear

Characteristics of included studies (*Continued*)

Study	**Morice 2001**
Methods	The subjects were randomized into two groups: one receiving subsequent visits from the asthma nurse until discharge from hospital (n = 35) and a control group (n = 30) which received 'routine care' from medical and nursing staff but no further intervention from the asthma nurse.
Participants	A group of 80 patients (53 women), with an age range of 16 to 72 years (mean 36.1 years) was recruited. Patients who had been admitted on the general medical take to a large teaching hospital with a documented primary diagnosis of acute asthma were recruited for the study. Patients were not permitted to participate if they: (1) had underlying chronic obstructive pulmonary disease; (2) had previously participated in an educational programme from a hospital-based asthma nurse; (3) were unable or unwilling to complete a series of follow-up questionnaires.
Interventions	The education programme took place over a minimum of two separate sessions, lasting on average 30 minutes each and was carried out on an individual basis. The first session involved discussion on the basic mechanisms of asthma, including common triggers and an explanation of the changes which occur to the airways resulting in the symptoms experienced by the patient. This was supported by illustrations in the 'Regular Therapy with Asthma' booklet (11) which was given to each intervention group patient. Lifestyle influences, such as occupation and leisure activities were discussed where appropriate to the individual. The need for 'preventer' and 'reliever' medication was also emphasized during this session. Patients were encouraged to actively participate in the session and relatives were included at the patients' request. The second session took place on the following day. Previously given information was briefly summarized with input from the patient as a means of checking understanding. An agreed individualized self-management plan was determined, with written instructions using the 'Sheffield Asthma Card'. This also contained a telephone contact number. Each patient was given a peak low meter to take home and instructions on monitoring, with documentation of predicted peak low measurement and parameters for altering treatment, as well as clear written guidelines on when to seek emergency care. Home intervention was based upon a combination of symptoms and peak low recordings and all guidance offered throughout the educational programme was based on the British Thoracic Society (BTS) guidelines for the management of asthma in adults (3). A final visit was made to each patient where possible prior to discharge at which they were encouraged to express any fears or anxieties relating to their home managements.
Outcomes	Compliance was measured by questionnaire at 6 months. Clinical Health Outcomes included: (1) Occasions of GP call-outs and Re-admission; (2) Patients percentage of claiming to have a writing management plan; (3) Percentage of the compliance of using ß-agonist inhaler regularly everyday; (4) first line action.
Notes	
Allocation concealment	D – Not used

Study	**Nazareth 2001**
Methods	Patients were independently randomized by the health authority's central community pharmacy office using computer-generated random numbers. 165 patients were eligible at baseline in the intervention group and 151 patients were eligible in the control group. They used blocked randomization, stratified by trial centre, to ensure equal numbers of participants in each randomized group.
Participants	From June 1995 to March 1997, patients discharged from elderly-care wards were asked by the hospital pharmacist to give informed consent. 362 patients were recruited. Patients over 75 years who were taking four or more medicines at discharge were asked to join the study. Patients who could not speak English or were too ill were excluded.
Interventions	Between 7 and 14 days after discharge, community pharmacists visited the patients at home. This visit allowed the pharmacist to check for discrepancies between the medicines the patient was taking and those prescribed on discharge. The pharmacist assessed the patient's understanding of and adherence to the medication regimen and intervened when appropriate. Interventions included counseling patients or carers on the purpose and appropriate doses of the medication, disposing of excess medicines and liaising with general practitioners. The pharmacists arranged further community visits at their discretion. All assessments and interventions were sent to the hospital-based liaison pharmacist. A revised care plan was issued if a patient was re-admitted

	to hospital during the 6-month study period. Patients randomized to the control group were discharged from hospital following standard procedures. These included a discharge letter to the general practitioner who indicated the diagnosis, investigations and current medications. The pharmacists did not provide a review of discharge medication or follow-up in the community.
Outcomes	Compliance measures were made at baseline and at follow-up (3 and 6 months after start of intervention). The primary outcome was re-admission to hospital in the follow-up period. Secondary outcomes were number of deaths, attendances at hospital outpatient clinics and general practice (at home or in the surgery) and days in hospital as a percentage of days of follow-up.
Notes	
Allocation concealment	B – Unclear

Study	**O'Donnell 2003**
Methods	Random allocation of consenting patients to compliance therapy or control groups using odd and even digits from a standard random numbers table. The researcher obtaining outcome measures was blinded to the intervention.
Participants	54 of 96 consecutive people with psychosis, who had been admitted to St. John of God Hospital, Dublin, agreed to join the study. Patients aged 18 to 65 years, an IQ greater then 80, fluent in English, with no evidence of organic disturbance and diagnosed with schizophrenia. Each person who signed for informed consent took part in a structured clinical interview to determine their diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders.
Interventions	The control group received non-specific counseling compromising of 5 sessions lasting 30 to 60 minutes. The experimental group received 5 sessions of compliance therapy, each session lasting 30 to 60 minutes. The sessions covered a review of the patient's illness history, understanding of the illness and his or her ambivalence to treatment, maintenance medication and stigma. Compliance therapy is a cognitive behaviour intervention with techniques adapted from motivational interviewing, other cognitive therapies and psychoeducation.
Outcomes	A structured clinical interview was used to assess compliance 1 month before the intervention and 1 year post-intervention. Patient outcome measures included attitude towards medication, symptomatology, insight, functioning, quality of life and psychiatric hospital bed occupancy. The following scales were used: DAI - Drug attitude inventory; PANSS - positive and negative symptom scale; SAI - Schedule for assessment of insight; GAF - global assessment of function; QLS- Heinrich's quality of life scale.
Notes	
Allocation concealment	B – Unclear

Study	**Odegard 2005**
Methods	A total of 77 patients were randomized, with 34 in the usual-care group and 43 in the pharmacist-provider intervention group.
Participants	Eligible patients included all adults at least 18 years of age and older with type 2 diabetes, taking at least one oral diabetes medication, with a glycosylated haemoglobin (HbA1c) result > or = to 9%. Non-English speaking subjects, those with unstable psychiatric conditions, or patients with a terminal prognosis within 6 months were not eligible.
Interventions	The pharmacist intervention entailed the development of a diabetes care plan (DCP), regular pharmacist-patient communication on diabetes care progress, and pharmacist-provider communication on the subject's diabetes care progress. Medication-related problems requiring intervention were identified as part of the DCP. The pharmacist intervention was initiated one week after the baseline interview with an in-person appointment to develop the DCP that was then communicated to the primary care provider using electronic notation in the medical record. The pharmacist maintained regular contact with the subjects with weekly in-person or telephone meetings. Once the patient and pharmacist determined that the diabetes care needs were progressing as outlined in the DCP, follow-up phone call frequency was reduced to monthly through

	the 6-month intervention period. Patients in the usual-care group were instructed to continue normal care with their primary care provider.
Outcomes	HbA1c was used as the clinical endpoint and assessed at baseline, 6 months, and 12 months. Diabetes knowledge and quality of life with diabetes were assessed using a brief sample of questions used for identifying opportunities for diabetes care support and developing the DCP. Diabetes care history, adherence challenges, self-management skills, and diabetes knowledge were assessed at baseline during an in-person interview. Medication appropriateness of all prescribed drugs was assessed from the medical record by the Medication Appropriateness Index (MAI). Adherence was assessed at baseline, 6 months, and 12 months using a self-reported, 2-question recall technique. Medication use history was collected at baseline, 6 months, and 12 months.
Notes	
Allocation concealment	B – Unclear

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 – Unclear

Study	**Peterson 2004**
Methods	Random allocation, not otherwise specified.
Participants	210 eligible patients with established cardiovascular disease and an acute cardiovascular /cerebrovascular-related admission, and discharged from the hospital between April and October 2001 on statin therapy, were invited to participate in the study. Patients were excluded if they had dementia, lived in a domiciliary care facility or lived beyond the greater Hobart area. Ninety-four provided informed consent. Thirteen patients were subsequently lost to follow-up; six from the control group and seven from the intervention group.
Interventions	Patients in the intervention group were visited at home monthly by a pharmacist, who educated the patients on the goals of lipid-lowering treatment and the importance of lifestyle issues in dyslipidaemia and compliance with therapy, assessed patients for drug-related problems, and measured total blood cholesterol levels using point-of-care testing. Patients in the control group received standard medical care. There was no further contact with patients in the control group after the initial collection of baseline data, until 6 months had

	lapsed. At that time, their final total blood cholesterol level was measured, and the current medication regimen and self-reported compliance were recorded.
Outcomes	Self-reported compliance at 6 months. Measurement of Clinical Health Outcomes: the total cholesterol levels.
Notes	
Allocation concealment	D – Not used

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 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 Medication Event Monitoring System (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 – Adequate

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, caregivers, 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 over 75 years of age, had a diagnosed psychotic disorder, disabling sensory impairment, or life expectancy of less than 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 months), 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 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 Healthcare 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 – Adequate

Study	**Portsmouth 2005**
Methods	Patients (n = 43) were randomized at baseline to receive treatment in one of two dosing regimens: patients in the intervention (or PRC) group (n = 22) were assigned to take Stavudine d4T PRC/3TC/EFV all once-daily (24 hours apart) and patients in the usual care group (n = 21) were assigned to continue the twice daily version of d4T (IR/3TC/EFV or Combivirs/EFV) as per their screening regimen.
Participants	Patients were over 18 years of age and weighed over 40 kilograms. Patients were excluded from this study if they were pregnant (in women of childbearing potential, consent was obtained to ensure they used two effective forms of contraception and regularly underwent urinary pregnancy testing), they had proven or suspected hepatitis, an active AIDS-defining disease, a history of bilateral peripheral neuropathy or signs of bilateral peripheral neuropathy of grade 2 or higher.
Interventions	This intervention involved simplifying the dosage for a nucleoside reverse transcriptase inhibitor (NRTI) from twice-daily to once-daily. Patients in the intervention group were assigned to take Stavudine d4T PRC/3TC/EFV all once-daily (24 hours apart). Control group patients continued either d4T IR/3TC/EFV or Combivirs/EFV as per their screening regimen.

Outcomes	Compliance was measured using the information obtained from Medication Event Monitoring System (MEMS) caps given with the medication and downloaded at baseline, week 12 and week 24 visits. Three compliance summary variables were computed: 1) taking compliance, the percentage of prescribed number of doses taken; 2) correct dosing compliance, the percentage of days with correct number of doses taken; and 3) timing compliance, the percentage of doses taken within + 3 h of the prescribed dosing intervals. At each visit, a clinical history was taken and a clinical examination was performed that entailed searching for symptoms of peripheral neuropathy, an examination of peripheral sensation, motor power and reflexes, checking viral load , total lymphocyte and subset analysis, full blood counts and measurements of serum transaminases (including gamma glutamyl transferase (g-GT), serum amylase, lactate and anion gap), total cholesterol, triglycerides, low-density lipoproteins (LDL), high-density lipoproteins (HDL), serum electrolytes, and urea and creatinine. At baseline, week 12 and week 24, a quality-of-life assessment was made using a Medical Outcomes Study HIV Health Survey (MOS-HIV) questionnaire.
Notes	
Allocation concealment	B – Unclear

Study	**Pradier 2003**
Methods	RCT: Patients were randomized into the intervention group (IG) and the control group (CG).
Participants	All HIV-infected patients who had medical follow-up at the Nice University Hospital between September 1999 and December 1999 were approached for the study participation. Patients were included if they were: 1) over 18 years of age; 2) Being treated for at least 1 month by a combination of at least 1 protease inhibitor (PI) or 1 nonnucleoside reverse transcriptase inhibitor (NNRTI) or abacavir with 2 nucleoside reverse transcriptase inhibitors (NRTIs); 3) Not having required hospitalization in the prior month or requiring it at the time of consultation; 4) Not being previously included in another protocol.
Interventions	The intervention combined an educational and counseling approach that was founded on the principles of motivational psychology, client centred therapy and the use of an "empathic therapeutic to enhance participants' self efficacy". The intervention focused on cognitive, emotional, social and behavioural determinants affecting adherence. The intervention consisted of 3 individually delivered sessions by nurses lasting 45 to 60 minutes. To standardize the intervention, intervention group manuals for the nurses were prepared and the nurses attended a 5-day intensive training course given by psychologists. Some flexibility was allowed for the nurses to tailor the intervention based on the needs of the individual patient. To ensure the quality of the intervention each nurse had supervision sessions with a psychologist and a clinical supervisor to review written material filled out by the nurses. No mention was made of the care that was provided for the control group.
Outcomes	This data was collected using a self-administered questionnaire at month 0 (M0) and month 6 (M6). Measurement of Clinical Health Outcomes: 1) Change in Viral Load between M0 and M6; 2) Percentage of patients achieving plasma HIV-1 RNA levels < 40 copies mL at M6; 3)16-item HAART related symptom scale; 4) Proportion of patients with reported toxic events; 5) Depressive mood using CES-D scale.
Notes	The clinical significance of these findings is unclear - adherence rate was on self-report in an unblinded trial, the mean HIV RNA was no different at 6 months for the 2 groups and no actual clinical outcomes were reported.
Allocation concealment	B – Unclear

Study	**Ran 2003**
Methods	Cluster RCT: A random numbers table achieved block randomisation using townships as units. Xinle and Huaqiao were randomly selected into the family intervention group (FIG) (drug treatment plus psychoeducational family intervention), Anxi and Taiping townships into the drug treatment group (MG) (drug treatment only), and Xinyi and Longma townships into the control group (CG) (no intervention).

Characteristics of included studies (*Continued*)

Participants	357 persons with schizophrenia from the six townships meeting the inclusion criteria were randomized. In fact, 127 received intervention (FIG) 105 patients received medication (MG) and 115 received no intervention (CG).
Interventions	The interventions were as follows: 1. Family education conducted once per month for 9 months. The purpose was to provide specific advice, support and information to the family. During each visit, which lasted 1.5-3 h, patients' relatives were taught basic knowledge of mental diseases, treatment and rehabilitation. Advice and information were given according to the patient's specific condition, such as the stage of illness, recent onset or chronic. The patient was encouraged to join the meeting. The major content of the family education component included: a) definitions of a schizophrenic disorder; b) a description of the various symptoms; c) comprehensive basis of the illness; d) general prognosis of the illness; e) treatment recommendations concerning pharmacotherapy; and f) long-term management of the illness including relapse prevention and social functioning rehabilitation. 2. Multiple family workshops were held once every 3 months. During the workshop, general questions were discussed, and relatives shared the experiences of caring for patients. 3. Crisis intervention conducted when necessary (e. g. for attempted suicide, aggressive and destructive behaviour). The local village broadcast network was also employed for health education during the first 2 months. Trained psychiatrists and village doctors conducted all these above-family interventions. Village doctors did not get the same training as psychiatrists, but assisted with the interventions. The drug treatment consisted of long-term injection of haloperidol decanoate (50 to 125mg/month) and/or an oral depot. There was no significant difference of drug dose between the family intervention group and the drug treatment group.
Outcomes	Medication compliance was defined as the therapist's dichotomous rating (based on all available information) of the extent to which the patient takes his/her neuroleptic medication consistently. Fifteen independent researchers, each of whom conducted assessments in all six townships, conducted the assessment. Patient outcome measures included clinical status, relapse rate, ability to work, mental disability.
Notes	Although there was contamination bias between MG and CG (the participants might go to see the other doctors in local area and then take medication by themselves), it didn't impact the comparison between FIG and MG.
Allocation concealment	D – Not used

Study	**Rawlings 2003**
Methods	Consenting patients were randomized 1:1 to receive either: an EI (4 modules of the Tools for Health Empowerment course) plus routine counseling (RC) (EI + RC); or RC alone.
Participants	A 24-week open-label clinical trial was conducted in 195 HIV-infected adults commonly underrepresented in research (35% female, 71% African American, 21% Hispanic, and 20% injection drug users [IDUs])
Interventions	The THE course is an 11-module educational program for HIV-infected patients and their informal caregivers in which there are interactive small arm sessions facilitated by a healthcare professional trained in the principles of adult learning, skills-building exercises aimed at behavior change in participants, flip charts, videotapes, patient logbooks, and patient workbooks. Program materials are designed at a fifth-grade reading level (English only). The goal of the THE course is to empower people living with HIV/AIDS and their informal caregivers with the knowledge, skills, attitudes, and resources to improve self-care, adherence, quality of life, and satisfaction with care, leading to improved quality of care. The following 4 modules focusing on patient empowerment, HIV pathogenesis and treatment, and medication management and adherence were delivered (1 session per week) during weeks 1 through 4 of this clinical trial. "The RC consisted of provision of the following information at each study visit: names and physical descriptions of the study drugs; instructions on how best to take the study drugs, including dosage and dosage schedules (taking the patient's daily routine into account) as well as how/when to remove the medications from bottles using Medication Event Monitoring System (MEMS) TrackCaps (APREX Corporation, Union City, CA); importance of taking the study drugs exactly as prescribed; and potential adverse events as well as actions to take if study participants experienced any of these".

Outcomes	Adherence was measured using MEMS track caps which monitored and electronically recorded the date and time each medication was removed from the bottle. The primary efficacy measure was the proportion of patients attaining plasma HIV-1 RNA levels below the 40-copy/mL lower limit of quantitation (LLOQ) of the NucliSens assay and below the 400-copy/mL LLOQ of the HIV-1 MONITOR version 1.0 polymerase chain reaction (PCR) assay (Roche, Nutley, NJ) at 24 weeks after starting treatment with COM + ABC. Viral load response (HIV-1 RNA in plasma) was the primary study end point. A secondary efficacy measure was an assessment of changes in the number of CD4 lymphocyte counts (immunologic response). Patients were also monitored for adverse events, lab abnormalities and HIV-related illnesses at week 5, 8, 12, 16 and 24.
Notes	
Allocation concealment	B – Unclear

Study	**Razali 2000**
Methods	The selected patients were randomly assigned to the study group (n = 80), which received the culturally modified family therapy (CMFT), or control group (n = 86), which received the behavioral family therapy (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 to 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 Brief Psychiatric Rating Scale (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 the Global Assessment of Function (GAF) of DSM-IV, while the Social Behavior Schedule (SBS) measured the behavioral difficulties.
Notes	
Allocation concealment	B – Unclear

Study	**Remien 2005**
Methods	Couples (n = 215) were randomly assigned to one of two groups: the four-session couple-focused adherence program (n = 106), or usual care through the medical provider of the HIV-sero-positive partner (n =

	109). A randomization table was constructed from a random numbers list and stratified by couple type. Randomization was conducted by the study's project director while assessors and all other personnel (except for intervention facilitators) were blind to study arm assignment throughout the trial.
Participants	Patients were eligible if they were an HIV-sero-discordant couple (self-report) with a relationship duration of 6 months or more, and both partners were English-speaking adults (over 18 years of age). The HIV-sero-positive partner needed to be in primary care and taking anti-retroviral therapy (ART) for at least 1 month. Couples meeting these criteria were scheduled for an in-person main screening appointment where the couple's relationship status was confirmed by independently asking each partner when and how they met, whether they considered themselves to be in a 'committed' relationship, and whether they expected to be in this relationship for at least another year. Couples returned 2 weeks later and were eligible for the study if less than 80% of prescribed doses were taken within specified time windows during the 2-week Medication Event Monitoring System (MEMS) observation period.
Interventions	The intervention, a four-session couple-focused adherence program, aimed to improve patients' adherence to HIV/AIDS medical care regimens by fostering the support of their partners; as well, to help couples address their issues of sex and intimacy. The intervention was individually administered to each couple by a nurse practitioner through four 45 to 60 minute sessions held over 5 weeks. The session content included structured discussions and instruction, as well as specific problem solving and couple-communication exercises. Key components included education about the importance of adherence to avoid viral resistance and maintain health, identifying patterns of non-adherence, developing communication and problem-solving strategies to overcome adherence barriers, optimizing partner support, and building confidence in the couple for achieving and maintaining improved adherence. Standard care patients received attention to adherence-related issues from a multidisciplinary treatment team. Dosing, common side effects, and the importance of adherence to the regimen as prescribed were discussed. Patients were instructed to contact the clinic to speak with either their medical provider or a nurse if they have difficulties with the regimen. Follow-up with the patient's medical provider usually occurred within 2 to 4 weeks after initiating a new regimen. Any adherence problems were assessed in order to find the underlying causes and the appropriate manner to address them.
Outcomes	The primary measure of adherence was the MEMS cap. MEMS data were downloaded into computer software to calculate adherence summary scores for the percentage of prescribed doses taken (without regard to timing) and the percentage of prescribed doses taken within specified time windows (e.g., for twice-a-day regimens, intended dosage times were set 12 hours apart, with ± 2 hour windows around each intended dosage time). The adherence summary scores were adjusted through participant self-reports of errors in MEMS use. Viral HIV RNA load and CD4 cell count assays at baseline and at week 8 were used as clinical measures. If a blood sample was not given, the patient's medical chart was examined for clinical outcomes within appropriate time intervals. If neither a blood sample nor medical chart data was provided, self-reported biomarkers were used.
Notes	
Allocation concealment	A – Adequate

Study	**Rickles 2005**
Methods	Randomization involved the researcher preparing 10 pieces of paper with sequential numbers for each participating pharmacist at the site. Each of the eight pharmacies had a different cluster of numbers. When a patient was enrolled form a site, the researcher would randomly select a number out of the envelope. Selection of an odd or even number meant the patient was assigned to the control group or the intervention group, respectively. A total of 63 patients were randomized to either the intervention group (n = 31) or the control group (n = 32).
Participants	Patients were 18 years of age or older, willing to pick up their medication from a study pharmacy during the next four months, having no hearing impairment, having no antidepressant use in the last 4 months and planning to be in the local area in the next 4 months. Patients excluded from the study were those with a Beck Depression Inventory Second Edition (BDI-II) score below 16, requiring a translator, pregnant

	or nursing, receiving medications for a psychotic or bipolar disorder, and/or having physical conditions requiring additional caution with their antidepressant.
Interventions	Patients in the intervention group received 3 monthly calls from the pharmacists providing pharmacist-guided education and monitoring (PGEM). On average, the first telephone call took place within the first 3 weeks of the patient picking up their initial antidepressant prescription from the pharmacy and took ~19 minutes to complete. During the first call, the pharmacist assessed the patient's antidepressant knowledge and beliefs and clarified or explained issues that were not understood by the patients. Pharmacists rated the severity of their concerns and made suggestions on how to handle adverse effects, difficulties remembering or paying for medications, and other concerns. Also, the pharmacists accessed the patient's treatment goals or areas in which they hoped the medication would help, and how the medication was being used during the week before the telephone call. Pharmacists were expected to follow up on any indication of medication non-adherence, inquire on why the doses were missed and make recommendations to increase medication compliance. The second and third telephone calls took place approximately 1 and 2 months after the initial call and on average, required 12 and 11 minutes to complete. During these calls, study pharmacists used the monitoring tool to guide their follow-up on any concerns identified in earlier calls and made new recommendations as needed. Pharmacists reviewed current adherence, whether any new adverse effects or concerns had developed, and evaluated the patient's progress in their medication goals. Patients in the control group received 3 monthly calls from the pharmacists providing usual pharmacist's care- defined as that education and monitoring which pharmacists may typically provide patients at the study pharmacies.
Outcomes	Medication adherence was recorded after the first 3 months after enrollment and again, after another 3 months. The number of missed doses was calculated by multiplying the number of prescribed doses per day times the number of days late between refills for the first 3-month period and second 3-month period. Results were multiplied by 100 to yield the percentage of missed doses for each period. The pharmacy records used for this method of compliance measurement was validated in two ways. First, the pharmacy records were compared with prescription insurance claims for 49 of 63 patients for whom claims data were available from the participating managed care organization. Inconsistencies were resolved by the research pharmacist after case-by-case analysis. Second, the patient's self-reported antidepressant adherence was measured as part of the outcomes survey, "In the past 7 days ending yesterday, how many times did you miss taking a pill?" The BDI-II was used to measure depression symptoms.
Notes	While pharmacist-guided education and monitoring had no significant impact on adherence at 3 months, a per-protocol analysis revealed significantly improved adherence at 6 months for those who completed the study. When the three patients who withdrew from the study were included in the analysis, the difference did not reach significance at the .05 level.
Allocation concealment	C – Inadequate

Study	**Rudd 2004**
Methods	Eligible patients underwent randomization using computer-generated assignment to receive either usual medical care only (UC; n = 76) or usual care plus nurse care management intervention (INT; n = 74). At 3 and 6 months after randomization, a research assistant blinded to group assignment measured clinic blood pressure (BP) and interviewed patients about medications taken since the previous visit.
Participants	Patients had an elevation of BP to levels greater than 150 mm Hg systolic, 95 mm Hg diastolic, or both. This was confirmed by the mean of two BP values being greater than 150/95 mm Hg on two screening visits conducted on separate days at least 1 week apart.
Interventions	The intervention consisted of the nurse care manager conducting baseline counseling on the correct use of the automated BP device, regular return of the automatically printed BP reports, tips for enhancing drug adherence, and recognition of potential drug side effects. The nurse initiated follow up phone contacts at 1 week and at 1, 2, and 4 months that averaged 10 minutes in duration. During the phone calls, the nurse asked the patients about each medication dosage and any problems experienced since the previous contact. Patients were encouraged to telephone anytime during regular hours with questions or concerns. The nurse care manager contacted physicians to obtain permission to initiate any new BP drug but did not

	contact physicians regarding changes in medication dosage. Usual care in both groups consisted of patients continuing to receive the routine care that they had received before the study.
Outcomes	Compliance was measured in both groups from the data downloaded using the electronic drug event monitors (eDEMs). The same semi-automated portable device was used to measure BP at home and during each clinic visits. At home, patients recorded BP twice-daily at the same times each day and each week, the device generated a printed report of up to 14 measurements.
Notes	
Allocation concealment	B – Unclear

Study	**Sackett 1975**
Methods	Random allocation, 2 x 2 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 – Unclear

Study	**Sadik 2005**
Methods	Patients (n = 221) were randomized to either the intervention group (n = 109) or control group (n = 112) using the minimization method. Both groups were matched as closely as possible, for the following parameters: severity of heart failure (HF) (NYHA Grade I- IV), renal function (serum creatinine > or = to 200 mmol l-1 or < 200 mmol l-1), other concomitant illness and cognitive status (CAPE survey score). No method of allocation concealment was mentioned.
Participants	Patients had a diagnosis of heart failure, a score of more than 6 on the Clifton Assessments Procedures for the Elderly (CAPE) survey used to assess cognitive status, and the consent of a hospital consultant for the trial. Patients were excluded from the trial if they had significant airways disease and severe mobility problems due to other causes.
Interventions	Patients receiving the intervention were 1) educated on heart failure (HF), their prescribed medication and the management of HF symptoms by the research pharmacist; 2) given a printed booklet developed for this type of education programme, which contained information on HF, its symptoms, the aims of treatment, the types of medication used and their possible side-effects, diet and lifestyle changes, advice to stick to one brand of digoxin (it having a narrow therapeutic index) and information on the action to take if doses of medication were missed; 3) instructed on a self-monitoring programme (signs and symptoms of HF; compliance with prescribed medication) in which they were asked to become engaged and involved a monitoring diary card

	(covering 1 month); 4) asked to record their weight daily in their diary card because they had been instructed to take an extra dose of their diuretic and to contact their physician immediately if their weight increased by 3 kilograms over 48 hours or if there was a marked deterioration in their HF signs/symptoms; 5) asked to perform daily exercise (walking); and 6) given rationalization of drug therapy or simplification of dosage regimens, when deemed appropriate. Control group patients received usual care, i.e. excluding counselling and education by the research pharmacist, self-monitoring, pharmacist liaison with physicians, etc.
Outcomes	At the 3-monthly outpatient clinics patients were assessed as per initial baseline assessments as follows: 2-minute walk test (including time to walk 25 and 50 metres), blood pressure, body weight, pulse, forced expiratory vital capacity (FVC), quality of life questionnaires (MLHF questionnaire and the SF36), questionnaire on symptoms and knowledge of, and compliance with, prescribed medication and lifestyle advice.
Notes	
Allocation concealment	B – Unclear

Study	**Samet 2005**
Methods	Patients (n = 151) were randomly assigned to either the control (n = 77) or intervention group (n = 74) and balance between groups was ensured every 4 subjects that were enrolled.
Participants	Patients were HIV-infected and had a history of alcohol problems. HIV status was confirmed by laboratory tests and alcohol problems were defined as current or lifetime history of alcohol abuse or dependence and were determined by two or more positive responses to the CAGE alcohol screening questionnaire. Those who did not meet the CAGE criteria were eligible if one of two attending physicians made a clinical diagnosis of alcohol abuse Patients also were fluent in English or Spanish, had a Mini-Mental State Examination score of at least 21 or greater and had no plans to move from Boston area in the following 2 years.
Interventions	The intervention (called ADHERE) incorporated 4 distinct components: 1) assessment and discussion of the patient's alcohol and other substance use based on stage of readiness for behavioural change; 2) use of a watch as a medication timing device to improve adherence; 3) enhancement of perceived efficacy of medications; and 4) individualized HIV counseling and exploration of ways to tailor medication use to specific circumstances. Visits for the intervention group was scheduled for an initial 60-minute appointment (within 2 weeks of randomization), a follow-up home visit within the first 3 weeks and two subsequent 15 to 30 minute appointments at 1 month and 3 months with the nurse interventionist who delivered the adherence enhancement intervention. Patients in the control group received standard care for HIV infection, which included verbal or written instructions about optimal medication strategies and regular medical care for HIV infection.
Outcomes	Adherence to anti-retroviral therapy (ART) was measured using the AIDS Clinical Trials Group (ACTG) scale for both the previous 3 days and 30 days. Self-reported adherences were measured using the ACTG scale. Adherence was defined as > 95% adherence over the previous 30 days and 100% adherence over the previous 3 days. In addition to the dichotomous measure of adherence, a continuous measure of adherence for the past 30 days was measured using the actual proportion of doses taken verses doses prescribed. Both adherence outcomes were assessed at 6-months (short-term) and at 13-months or 12 months (long-term). Self-reported adherence assessment was verified with the MEMS caps of certain patients- ones who reported no change in HIV medications during the assessed interval and did not use a pill-organizing container. At 12 months, the following clinical outcomes were assessed: 1) CD4 cell count; 2) Log HIV RNA; and 3) Alcohol severity and consumption (using both the Addiction Severity Index and quantity and frequency questions assessing the previous 30 days), which was used to calculate the average number of drinks per day.
Notes	
Allocation concealment	B – Unclear

Study	**Schaffer 2004**
Methods	Participants were recruited using flyers posted throughout the health science center campus, within the university student health center, and in health departments within the county. In an effort to approximate the ethnicity of the surrounding county, which is 19% African American, the principal investigator also

	recruited participants personally in an African American church. There were 46 participants at the beginning of the study. A computerized randomization protocol was used to assign participants to one of 4 treatment groups.
Participants	There were 46 participants at the beginning of the study. English-speaking adults aged 18 to 65, whose reported use of preventive medication for asthma during the 3 months prior to the study indicated that they had mild persistent to moderate persistent asthma according to the U.S. NAEPP (2002) guidelines. Individuals were excluded if they reported daily oral steroid use, diagnosis of chronic obstructive pulmonary disorder (COPD), or symptomatic cardiac disease.
Interventions	Four treatment groups: (a) standard provider education (control) (n = 13); (b) audiotape alone (n = 10); (c) National Heart Lung and Blood Institute (NHLBI) booklet alone (n = 12); and (d) audiotape plus NHLBI booklet (n = 11).
Outcomes	Compliance Measurements: self-reported and pharmacy verified adherence to preventive medication. Measurement of Clinical Health Outcomes: Asthma control measured with the Asthma Control Questionnaire (ACQ), asthma quality of life measured with the Mini Asthma Quality of Life Questionnaire (MiniAQLQ), and asthma self-efficacy assessed using the Perceived Control of Asthma Questionnaire (PCAQ). Asthma knowledge was measured with the Asthma Knowledge Scale, developed for this study.
Notes	The ACQ is a 7-item Likert-type scale designed to measure asthma treatment adequacy as measured by minimization of symptoms, bronchoconstriction, and short-acting beta-agonist use.
Allocation concealment	A – Adequate

Study	**Schroeder 2005**
Methods	An author not involved in the practice and patient recruitment randomized eligible patients (n = 245) stratified by age and sex to the intervention (n = 128) and control (n = 117) groups, using computer-generated random numbers that were assigned to an anonymized list of participants. The principal investigator passed the randomization schedule on to the practice nurses shortly before the appointment for delivering the intervention. The study participants and the practice nurses were aware of the group assignment.
Participants	Patients had hypertension and a latest blood pressure recording of > or = to 150 mm Hg systolic and/or 90 mm Hg diastolic in the past six months. Patients were excluded from the study if they did not control their medication intake (such as some nursing home patients), had secondary hypertension, severe dementia or other reasons for not approaching them, such as recent bereavement.
Interventions	Patients in the intervention group received, in addition to usual care, a nurse-led adherence support session lasting a maximum of 20 minutes, followed by a shorter reinforcement session (10 minutes) two months later. The intervention was aimed to provide an opportunity for patients to talk about any problems with their blood pressure lowering medication. Practice nurses investigated whether patients understood their diagnosis and agreed with the treatment process. They also addressed patient concerns with their medication and to agree to tailored strategies to resolve any medication problems. The control group received standard care delivered at their respective practices, apart from blood pressure checks at similar intervals as the participants in the intervention group. Wherever possible, these checks were carried out by another practice nurse who was not involved in delivering the intervention but all practice nurses were made aware of the risk of contamination and encouraged not to change their 'usual practice' for the control patients.
Outcomes	The primary adherence outcome was measured by Medication Event Monitoring System (MEMS) in the six months period following the intervention. Adherence was defined as 'timing compliance', which is the number of doses taken at 24 ± 6 hour intervals for a once daily regimen or 12 ± 3 hours for twice daily doses, divided by the total number of days and multiplied by 100%. Two additional measures of adherence were taken: 1) 'correct dosing', which was the percentage of days on which the correct number of doses was taken; and 2) 'taking compliance', was defined as the percentage of prescribed number of doses taken, equivalent to a 'pill count'. Systolic and diastolic blood pressure was measured at baseline as well as 1, 2, and 6 months after randomization.
Notes	

Allocation concealment	A – Adequate

Study	**Stevens 2002**
Methods	Patients who tested positive for H pylori were randomly assigned to either usual care or special counseling using a computer-generated random sequence. The partcipating pharmacies were provided with a supply of opaque randomization envelopes, and the pharmacists were trained to open the top envelope to determine the treatment assignment for each research participant.
Participants	325 adult dyspeptic patients with positive for H pylori paricipated in the study.
Interventions	All the patients were provided a standard antibiotic regimen and randomly assigned to receive either usual-care counseling from a pharmacist (The control group participants met with the dispensing pharmacist for 5 minutes. The pharmacist described the proper protocol for taking the medication. This is consistent with standard care.) or a longer adherence counseling session and a follow-up phone call from the pharmacist during drug treatment (Patients received a 15-minute counseling session with the pharmacist, including a detailed review of possible side effects, emphasis on the importance about possible barriers to adherence and coping stratagies, and encouragement to call the pharmacist in the event of any problems. The pharmacist also scheduled a follow-up telephone call with the patient 2 to 3 days after the start of therapy to check on adherence to the drug regimen.). All subjects were given the same 7-day course of omeprazole, bismuth subsalicylate, metronidazole, and tetracycline hydrochloride (OBMT).
Outcomes	All the patients were contacted by telephone and were asked to report their adherence to regimen and their current symptoms.
Notes	The major problems with this study are that a) both groups received blister packs with daily doses clearly marked; b) both groups received counseling, although this was longer and more detailed for the intervention group than the control group; and c) self-report was used for measuring adherence (insensitive). All these factors would bias towards no difference.
Allocation concealment	A – Adequate

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 – Unclear

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.

	There is no statement in the report about blinding of physicians. Patients and psychologists were not blinded, and, if there was a separate outcome assessor, it is not stated.
Participants	116 patients who initiated their first or second-line highly active antiretroviral treatment (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 more than 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 – Unclear

Study	**Van Servellen 2005**
Methods	Participants (n = 85) were randomly assigned to receive the intervention program (n = 42) and the control group (n = 43), receiving standard clinic care only. Clinic medical records were screened by the clinical trials staff for eligible patients. Neither the method of randomization nor the allocation concealment was described.
Participants	All clinic medical records were screened by the clinical trials staff and were identified as eligible if the following criteria were met: male or female, 18 years or older, and had problems with medication adherence as charted in the patients medical record, Spanish-speaking, detectable viral load, and taking antiretroviral medications for at least 3 months. Patients were excluded if they had both a problem with adherence as well as a detectable viral load or were having adherence problems with undetectable viral loads. Being naive to medication, on or off medication, and numbers of previous medication combinations, were not considered in including participants. Changes in medication, discontinuation of a medication or the addition of another, did not constitute a reason to drop participants from the study. No patients were taken off antiretroviral therapy.
Interventions	The intervention consisted first of modular instruction that was provided by the nurse practitioner and health educators to group patients only and included 5 sequential sessions aimed at increasing patients' HIV knowledge and abilities to communicate with medical staff. After these modular sessions, phone call and face-to-face encounters with the nurse practitioner were conducted with participants where the focus was to address patients' risks for non-adherence using problem-solving and motivational interviewing strategies. These sessions included reviewing content not fully understood in the group sessions, identifying and problem-solving ways to lower barriers to change, and to adherence management, and identifying community, treatment, and social support services or referrals to help them to address barriers to adherence. Patients in the control group received standard clinic care only.

Characteristics of included studies (*Continued*)

Outcomes	Medication adherence self-efficacy was measured with the Adherence Baseline Questionnaire. Medication adherence was analyzed in a number of ways: 1) calculated as a percentage of those missing 2 or more doses in the last 24 hours and last 4 days; 2) the proportion of doses missed per day was calculated by dividing the number of doses they should have taken by the number they took for each of the 4 days. The average proportion for the 4 days was calculated by averaging the mean proportion of doses missed for all 4 days; 3). percentages of participants who missed on average greater than 10% or 5% of their medications during the last 4 days were calculated for both groups; and 4) dichotomous variables were created identifying those who had greater than 90% and greater than 95% adherence in the past 4 days. Medical records were used to assess CD4 count, viral load and viral log changes at baseline, 3 months, and 6 months. Medication adherence was collected in interviews with participants at baseline, at 6 weeks and at 6 months. Health status and disease progression were assessed with self-report and clinical laboratory information in the patients' medical charts. Self-reported health status was measured with an item assessing perceived level of general health status in the past week. HIV/AIDS disease and treatment knowledge and misconceptions were assessed using a 17-item survey.
Notes	When patients were initially screened they were included if they had a problem with adherence. These patients were then re-screened for eligibility based on viral load, and those with detectable viral load excluded. Those with adherence problems and without detectable viral load were included in the trial. In addition, there was a discrepancy of n = 1 in the reporting of results for the intervention and control group; however, this is not considered to be an important difference for the outcomes of the trial.
Allocation concealment	B – Unclear

Study	**Vergouwen 2005**
Methods	In this study the general practitioners (GPs; n = 30) were randomly assigned to either the Depression Care Programme (DCP; n = 16), or the Standard Follow-Up Programme (SFP; n = 14). Random treatment assignment was placed in advance in a set of sealed, opaque envelopes by an individual who was not involved in the opening of the envelopes. When a GP was randomized, the GP's name and the number of the envelope were recorded before the envelope was opened. There were a total of 211 patients, 101 from the DCP and 110 from the SFP. The number of patients analysed were n = 81 in the DCP group and n = 96 for the SFU group.
Participants	Patients were eligible for the study if they met the following criteria: primary diagnosis of depression fulfilling the criteria of a major depressive episode according to DSM-IV; at least 18 years of age; no renal or hepatic dysfunction. Subjects had to give written informed consent prior to participation and the MINI International Neuropsychiatric Interview was used for the diagnostic psychiatric screening. Exclusion criteria were: benzodiazepines not stabilized at a maximum level of 10 mg diazepam or equivalent rate at least 4 weeks prior to start of treatment; use of other psychopharmacological medication ; a history of schizophrenia or bipolar disorder ; previously unresponsive to selective serotonin reuptake inhibitor (SSRI) therapy (for depression or other indications) ; women who were pregnant, lactating or not using adequate contraconception; a history of seizures (except for febrile seizures in childhood); meeting DSM-IV criteria for substance abuse within 3 months prior to the start of the trial, respectively substance dependence within 6 months; any serious medical condition that would, in the opinion of the GP, preclude the administration of a SSRI; a current serious suicidal or homicidal risk in the GP's judgment; and current psychological or psychotherapeutic treatment.
Interventions	Depression care programme: Prior to every scheduled visit (7 visits in 26 weeks), the DCP patients received a newsletter by mail, which reviewed the biology and symptoms for depression, as well as the importance of antidepressant medication, and its effects and side effects. In addition, the need to continue treatment for up to 6 months, the value of social support, social stigmas and common misconceptions about depression were explained. Patients also were asked to complete homework assignments that involved: (1) fill out a questionnaire addressing the perceived costs and benefits of antidepressant medication, (2) to plan activities, and (3) to discuss their illness and treatment with significant others. Before each visit, the GPs received a summary of the content of the newsletter and the homework assignments and both patients and GPs were encouraged to discuss the topics and homework assignments during the visits. In particular, the GPs clarified the benefits of and perceived costs of taking antidepressant medication. Systematic follow-up programme:

	Patients and GPs in the SFP received no letters, homework, nor instructions. The SFP targeted only the structure of care: follow-up visits were scheduled and structured, and patients were assessed with the same frequency and with the same instruments as the patients in the DCP group.
Outcomes	Adherence with antidepressant medication was assessed during the visits at weeks 2, 6, 10, 14, 18, 22 and 26, by pill counts. When a patient did not return pills, the patient's self-reports were used. Early adherence was defined as > 70% medication intake during the first 10 weeks. Late adherence was defined as > 70% medication intake during the full 26 weeks. Clinical outcomes were measured using: (a) The MINI at baseline and week 26; (b) Clinical Global Impression (CGI) at baseline and all the following visits; (c) The Beck Depression Inventory (BDI) at weeks 2, 6, 10, 18 and 26; and (d) The Symptom Checklist-90-Revised (SCL-90 R) at weeks 2, 10, 18 and 26.The GPs did assessments of adherence, MINI, and CGI and the BDI and SCL-90 R were self-rating questionnaires.
Notes	
Allocation concealment	A – Adequate

Study	**Volume 2001**
Methods	Cluster randomized trial with pharmacies as the unit of randomization. Two of the 16 pharmacies were located two blocks apart in the same rural community. To minimize the risk of sample contamination between these two pharmacies, they were included in the same study group. One pair from the same community were assigned as a block. Eight pharmacies were randomly placed in the treatment group and 8 pharmacies were randomly to be in the control group. Pharmacists from five of the eight treatment pharmacies completed the practice enhancement program and began enrolling patients into the study.
Participants	Ambulatory elderly (> or = 65 years of age) patients (n = 60) covered under Alberta Health & Wellness's senior drug benefit plan and who were concurrently using three or more medications according to pharmacy profiles.
Interventions	In intervention group, pharmacists used the Pharmacist's Management of Drug-Related Problems (PMDRP) instrument to summarize the information collected during the patient interview and prepared a "SOAP" record (Subjective, Objective, Assessment, and Plan) to document actions and follow-up. Pharmacists at control pharmacies continued to provide traditional pharmacy care.
Outcomes	Adherence to medication regimens was assessed using a four item self-report measure. Health-related quality of life was assessed using the SF-36 health survey. The SF-36 has been used extensively to evaluate the success of clinical interventions.
Notes	
Allocation concealment	A – Adequate

Study	**Walley 2001**
Methods	RCT: individual patients were contacted by telephone through a third party (who was unaware of any information about the patient) at the research-team office, with a list of random allocations computer-generated by the research team. To allow for the possibility of failed telephone contact, facilities were also provided with pre-prepared allocations sealed in opaque envelopes. After randomisation, the enrolment officer and the patient discussed and agreed on the details of the selected treatment protocol.
Participants	497 patients were enrolled in the trial. Each adult (aged 15 years or older) whose initial diagnosis at the diagnostic centre was as a new case of sputum-positive pulmonary tuberculosis was sent to the enrolment officer who interviewed the patient to confirm eligibility for enrolment; in particular, to confirm that no treatment for tuberculosis had been taken previously, and that the patient lived in one of the trial catchment areas. Urban Rawalpindi was a WHO-sponsored "demonstration" site, patients in the demonstration site catchment area were excluded.
Interventions	170 were assigned DOTS with direct observation of treatment by health workers; 165 were assigned DOTS with direct observation of treatment by family members; and 162 were assigned self-administered treatment. The first, and prevailing, strategy was self-administered treatment, in which each patient collects drugs

	fortnightly from the most convenient health facility. The second was health-worker direct observation of treatment-ie, supervision by a health worker at a health facility when the patient met criteria for access to the facility, and by a community health worker at or near the patient's home otherwise. The access criteria, determined from the exploratory studies, were that the return journey from the patient's home to the health facility was a distance of less than 2 kilometres, a duration of less than 2 hours, and a cost of less than 10 rupees; and for unmarried women, an accompanying relative was to be available. The patient nominated the health facility most convenient for him or her. If the access criteria were met, a health worker at that facility was identified to supervise treatment; otherwise, a community health worker local to the patient's home and acceptable to the patient was chosen as supervisor. The supervisor was oriented on his or her role by a visiting field officer. The patient was then expected to attend the health facility or community health worker six times per week in the initial 2-month intensive phase to take the drugs. In the 6-month continuation phase, patients continued on self-administered treatment, collecting drugs fortnightly from the most convenient health facility or community health worker. The third strategy was family-member direct observation of treatment, that is, supervision by a family member. The patient was assisted in the selection of a concerned and influential family member as supervisor. The family member was oriented on his or her role. The patient (or family member) collected drugs fortnightly from the health facility most convenient for him or her. In both strategies involving direct observation of treatment, the supervisor was taught how to record drug-taking using a specially designed form, and was made aware of the importance of observing drug-taking and of encouraging the patient to complete treatment.
Outcomes	"Defaulted" in Table 2 as a proxy for "noncompliant". Default was defined as failing to collect treatment from the health centre for two consecutive months during the course of treatment. : The outcome measures used were cure, and cure plus treatment completion.
Notes	
Allocation concealment	A – Adequate

Study	**Weber 2004**
Methods	Random allocation, not otherwise specified.
Participants	60 HIV patients were randomized by the researchers after giving informed consent. Inclusion and Exclusion Criteria: therapy containing a combination of at least three different antiretroviral drugs of at least two different drug classes, viral load below 50 copies/ml documented within the previous 3 months and at screening visit, participation in the Swiss HIV cohort study, no intravenous drug use or on stable methadone maintenance in case of drug addiction.
Interventions	Participants were randomly assigned to a psychotherapist and given the contact information to schedule their own first appointment. Protocol defined a minimum of three and a maximum of 25 sessions within the 1-year study period. Participant and psychotherapist determined the frequency of appointments and set their own goals for future interventions. The method of intervention had to be based on concepts of cognitive behaviour therapy. Both intervention and control groups continued to receive standard care. Standard care included monthly visits for 12 months with assessments of clinical and laboratory data, course of treatment, drug adverse events and HIV-1 RNA.
Outcomes	An electronic medication exposure monitoring system was used to measure adherence. Outcome measures included virological and immunological outcomes, CD4 lymphocyte end-points, change in antiretroviral therapy during study, and psychosocial measures.
Notes	
Allocation concealment	A – Adequate

Study	**Weinberger 2002**
Methods	A cluster RCT: The 36 drugstores were divided into 12 clusters of 3 geographically proximal drugstores ("triplets"). The 3 drugstores within each triplet were matched on percentage of Medicaid-insured adults with reactive airways disease (to control for customers' socioeconomic status) and number of prescriptions

	filled (high versus low volume). Within each triplet, a random-number chart was used to assign drugstores to 1 of 3 study groups.
Participants	1113 eligible patients were enrolled. 453 were chronic obstructive pulmonary disease (COPD) patients and 660 people with asthma. Patients were censored from the study if they died, were placed in a nursing home, moved away permanently from Indianapolis, their insurance no longer covered using these drugstores, or they lost telephone access. Customers were eligible if they: (1) filled a prescription for methylxanthines, inhaled corticosteroids, inhaled or oral sympathomimetics, inhaled parasympathetic antagonists, or inhaled cromolyn sodium during the preceding 4 months; (2) reported having COPD or asthma as an active problem; (3) were 18 years or older; (4) received 70% or more of their medications from a single study drugstore; (5) reported no significant impairment in vision, hearing, or speech that precluded participation; (6) did not reside in an institution (eg. nursing home); and (7) provided written informed consent.
Interventions	Components of intervention in Pharmaceutical care program group (Group 1) included: 1) Computer Display of Patient-Specific Data. When a study patient filled any prescription (not only breathing medications), the drugstore computer alerted pharmacists to review patient-specific data contained in a separate study computer behind the counter. To safeguard patients' confidentiality, access to patient-specific data required pharmacists' individualized passwords. Study computers contained: (1) contact information for patients and 1 to 2 physicians caring for their breathing problem; (2) graphical display of all Peak Expiratory Flow Rate (PEFR) data gathered during monthly interviews; (3) dates and locations of recent emergency department visits and hospitalizations; and (4) breathing medications (including compliance rates and refill histories). These data were obtained during monthly telephone interviews. Pharmacists were encouraged to document their pharmaceutical care activities at the bottom of the screen. 2). Written Patient Educational Materials. One-page handouts were deveoped corresponding to specific problems associated with clinical data stored in the study computer. Handouts, designed to be easily understood by patients, used mnemonic devices and color coding to facilitate distribution by pharmacists. 3). Resource Guide. Attached to the study computer, guides contained laminated pages with practical suggestions to help pharmacists implement the program in a busy practice. 4). Pragmatic Strategies to Facilitate Pharmaceutical Care. To reinforce pharmacist training and facilitate program implementation: (1) pharmacists were encouraged to page the on-call investigator with questions; (2) an investigator made personal visits to each intervention drugstore every 1 to 2 months; (3) periodic newsletters containing information about reactive airways disease and suggestions on implementing the program were distributed; (4) weekly lists were faxed of recent patient activity (eg, medication refill, ED or hospital visit) and pharmacists' documented activities; and (5) pharmacists wre provided with telephone appointment scheduling cards to facilitate interactions with patients at a mutually convenient time. During the final year of the study, pharmacists were paid $50 per month for high rates of compliance with the pharmaceutical care protocol (viewing data on the study computer for 90% of patients and documenting actions for 75% of patients). Patients in the pharmaceutical care group received a peak flow meter, instruction about its use, and monthly calls from research personnel to obtain current PEFR results. The peak flow meter monitoring control group (group 2) also received a peak flow meter, instructions about its use, and monthly calls to elicit PEFRs. However, PEFR data were not provided to the pharmacist. Patients in the usual-care group received neither peak flow meters nor instructions in their use; during monthly telephone interviews, PEFR rates were not elicited. Pharmacists in both control groups also had a 4-hour training session although the topics were different and they received no components of the pharmaceutical care program .
Outcomes	Compliance measures were made at baseline, at 6 month and 12 months by face-to-face interview using 2 validated measures: a single-item indicator (proportion of noncompliance), and a 4-item scale ranging from 0 (low) to 4 (high) noncompliance. Self-report had been found to be valid when inquiries were made in a nonthreatening manner. Clinical Health Outcomes included: Peak expiratory flow rates, breathing-related emergency department or hospital visits, health-related quality of life (HRQOL), medication compliance, and patient satisfaction.
Notes	
Allocation concealment	B – Unclear

Characteristics of included studies (*Continued*)

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 to 17 years of age, having Type I diabetes for more than 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. 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 to 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-minute educational presentation by a diabetes professional, followed by a 45-minute 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 – Unclear

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 more than 50% of prescribed dosage was the measure for comparison of groups. Psychiatric outcomes were assessed at 6, 12, and 18 months following hospital discharge by observers who were trained clinical researchers, blinded to study group allocation.
Notes	
Allocation concealment	B – Unclear

Study	**Yopp 2004**
Methods	Following completion of this baseline assessment, adolescents (n = 53) were randomly assigned to either the standard care condition (n = 26) or the multisystemic therapy (MST) plus standard care condition (n = 27). The data collection staff worked independently from the MST intervention staff, and were blind to treatment conditions for the subjects.
Participants	Participating adolescents had: a) a diagnosis of type 1 diabetes for a minimum of one year; b) glycosylated haemoglobin (HbA1c) of at least 8% at the onset of the study; c) an average HbA1c of at least 8% for the previous year. Adolescents were excluded from the study if they: a) were unable to speak English; b) had been diagnosed with a thought disorder, such as schizophrenia, or; c) suffered from an additional chronic illness that may interfere with conventional treatment for type 1 diabetes.
Interventions	Standard care consisted of receiving treatment from a multidisciplinary team. Adolescents and their families attended clinic appointments every 3 months to monitor the adolescent's health and were provided with traditional diabetes education services and eligible to be referred to community-based mental health agencies for psychological or adherence concerns. In addition to the standard diabetes care described above, adolescents and their families assigned to the MST intervention received approximately 7 months of this family-based treatment. The initial goals of treatment were to understand and form hypotheses as to what factors are maintaining the adolescent's poor health status. Interventions were then implemented to address these problematic areas, including problems with general and diabetes-specific family interaction patterns negatively impacting the adolescent's treatment adherence. Overarching goals of MST interventions often included increasing family cohesion and structure, as they relate to completing diabetes management tasks. A variety of behaviorally-based, action-oriented interventions may have been used during MST including parent management training, problem-solving skills training, and contingency management. Specifically, family-based interventions are designed to improve communication between family members regarding completion of adherence tasks, ensure adequate parental supervision of diabetes management behaviors, and provide family members with strategies to address general and diabetes-specific conflict situations. Overall, the goal of MST is to encourage parents to adopt an authoritative parenting style in which they are responsive to their adolescent's health needs, able to see clearly defined expectations for adherence behaviors, and able to enforce effective discipline strategies to address problematic behavior. Treatment was terminated when overarching goals were accomplished.
Outcomes	Compliance was measured using the 1) Diabetes Management Scale (DMS) and 2) The Twenty-Four Hour Recall Interview. Both were administered separately to the adolescent and parent.. Glycosylated hemoglobin (HbA1c) values were used as clinical endpoints.
Notes	
Allocation concealment	B – Unclear

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

	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 – Unclear

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 to 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 peak expiratory flow (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 approximately 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 Forced Expiratory Volume (FEV). Subjective severity of asthma was assessed by asking the participant one question with a 5-point scale (1 = not at all bothered, no symptoms, to 5 =

	severely bothered, unable to function). Morbidity variables (number of admissions to hospital, number of prescriptions or oral steroids for an exacerbation) were also recorded.
Notes	
Allocation concealment	A – Adequate

Characteristics of excluded studies

Study	Reason for exclusion
Adamian 2004	Confounded comparison groups.
Adams 2000	No intervention intended to affect adherence with prescribed, self-administered medications. No measure of treatment outcome.
Adams 2001	No intervention intended to affect adherence with prescribed, self-administered medications.
Adler 2004	Follow-up rate < 80%.
Al Rashed 2002	No measure of treatment outcome.
Al-Saffer 2005	Follow-up too short. Follow-up rate < 80%. Pseudo-randomization method. No measure of treatment outcome.
Allen 2002	No intervention intended to affect adherence with prescribed, self-administered medications.
Alves da Costa 2005	Follow-up too short.
Antoni 2006	Follow-up rate < 80%.
Arthur 2002	No intervention intended to affect adherence with prescribed, self-administered medications.
Atherton-Naji 2001	Follow-up rate < 80%.
Azrin 1998	Only 2 months of follow-up.
Baker 2001	No intervention intended to affect adherence with prescribed, self-administered medications.
Ball 2006	Follow-up rate < 80%.
Banet 1997	No measure of compliance with medication at baseline.
Barbanel 2003	No measure of medication adherence
Barcelo 2001	No intervention intended to affect adherence with prescribed, self-administered medications.
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.
Birtwhistle 2004	Confounded comparison groups.
Bisserbe 1997	Study duration too short.
Bodsworth 1997	No compliance data presented and < 80% follow-up.
Bonner 2002	Follow-up too short or on less than 80% of participants.
Bouvy 2003a	Follow-up too short or on less than 80% of participants.

Bouvy 2003b	Follow-up too short or on less than 80% of participants.
Brodaty 1983	Follow-up too short or on less than 80% of participants.
Brook 2002	Confounded comparison groups.
Brook 2003	No intervention intended to affect adherence with prescribed, self-administered medications.
Brook 2005	Follow-up rate < 80%.
Brotons 2005	No measure of adherence outcome.
Brown 1987	Missing description of disease outcome.
Brown 1997b	No measure of compliance with medications.
Browne 2002	Confounded comparison groups.
Buchanan-Lee 2002	No intervention intended to affect adherence with prescribed, self-administered medications.
Bukstein 2003	Confounded comparison groups.
Bungay 2004	No measurement of adherence.
Burkhart 2002	Only 5 weeks of follow-up.
Burnand 2002	10-week follow-up.
Caine 2002	Confounded comparison groups.
Cantor 1985	Follow-up too short or on less than 80% of participants.
Capoccia 2004	Confounded comparison groups.
Cargill 1992	Follow-up too short or on less than 80% of participants.
Carroll 2004	No intervention intended to affect adherence with prescribed, self-administered medications.
Celik 1997	Follow-up in < 80%.
Chaisson 2001	No measure of treatment outcome.
Cheng 2001	No measure of treatment outcome.
Cheung 1988	Confounded comparison groups.
Chien 2006	No measure of adherence outcome.
Chiou-Tan 2003	Confounded comparison groups.
Chisholm 2001	No measure of treatment outcome.
Choi 2002	Confounded comparison groups.
Clancy 2003	No measure of medication adherence.
Clarkin 1998	Less than 80% follow-up.
Clifford 2002	No intervention intended to affect adherence with prescribed, self-administered medications.
Cochran 1984	38 patients were randomized before consent. When consent was requested, only 28 (74%) agreed so that the maximum, follow-up was less than 80%. 2 additional patients dropped out after giving consent.
Cockburn 1997	Follow-up rate < 80%.
Cohn 2002	No intervention intended to affect adherence with prescribed, self-administered medications.
Colom 2003	No intervention intended to affect adherence with prescribed, self-administered medications.
Cooper 2004	No measurement of adherence.
Cordina 2001	Follow-up rate < 80%.
Couturaud 2002	Follow-up rate < 80%.
Cramer 2003	No intervention intended to affect adherence with prescribed, self-administered medications.
Crilly 2005	No measure of adherence outcome.
Crockett 2006	Follow-up too short.

Daley 1992	Missing description of disease outcome.
Datto 2003	Confounding of physician adherence intervention with patient adherence intervention.
De Jonghe 2001	Confounded comparison groups.
Dehesa 2002	Confounded comparison groups.
Deinzer 2006	No measure of adherence outcome.
Delaronde 2005	Follow-up rate < 80%. Pseudo-randomization method.
Demiralay 2002	Follow-up too short (only 2 months).
Demyttenaere 1998	Study too short duration.
Demyttenaere 2001	Confounded comparison groups.
DiIorio 2003	Follow-up too short (only 2 months).
Dittrich 2002	Confounded comparison groups.
Donadio 2001	No measure of medication adherence.
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.
Evers 2002	Confounded comparison groups.
Falloon 1985	Missing data on adherence.
Feinstein 1959	Confounded comparison groups.
Fennell 1994	Confounded comparison groups.
Finkelstein 2003	Confounded comparison groups.
Finley 2003	Confounded comparison groups.
Finney 1985	Follow-up too short or on less than 80% of participants.
Fisher 2001	No measure of treatment outcome.
Franchini 2006	Not randomized.
Francis 2001	No measure of treatment outcome.
Frangou 2005	Follow-up too short.
Freemantle 2002	No intervention intended to affect adherence with prescribed, self-administered medications.
Frick 2001	No patients are prescribed medication for a medical (including psychological) disorder.
Fujioka 2003	No intervention intended to affect adherence with prescribed, self-administered medications.
Fumaz 2002	Confounded comparison groups.
Gabriel 1977	Missing description of disease outcome.
Gallefoss 2004	Confounded comparison groups.
Garcao 2002	The intervention is confounded..
Garety 2006	Follow-up rate < 80%. No measure of adherence outcome.
Garnett 1981	Missing description of disease outcome.
Gibbs 1989	Missing description of disease outcome.
Gilfillin 2002	No measure of medication adherence.
Godemann 2003	No measure of treatment outcome.
Goodyer 1995	Follow-up too short or on less than 80% of participants.

Goujard 2003	Follow-up was < 80%.
Graham 2002a	Confounded comparison groups.
Graham 2002b	Only 4 months follow-up.
Grant 2003	Follow-up was < 80%.
Gupta 2001	No intervention intended to affect adherence with prescribed, self-administered medications.
Guthrie 2001	No measure of treatment outcome.
Gwadry-Sridhar 2005	Follow-up rate < 80%.
Hamet 2003	No measure of treatment outcome.
Hamilton 2003	No measure of treatment outcome.
Hammond 2001	No measure of medication adherence.
Hampton 2001	Confounded comparison groups.
Hardstaff 2003	No measure of treatment outcome.
Haubrich 1999	Less than 80% follow-up at 6 months.
Hayes 2003	Patients are not prescribed a medication.
Heard 1999	In addition to 3 asthma clinic sessions, a GP consultation (where medications could be potentially be altered) was added to the intervention group. Also, it is unclear whether medication adherence is actually measured (i.e. paper only states that 'medication use' is assessed).
Herschorn 2004	Follow-up rate < 80%. Follow-up too short.
Hertling 2003	Confounded comparison groups.
Hesselink 2004	Follow-up rate < 80%.
Hoffman 2003	No measure of treatment outcome.
Holzemer 2006	Follow-up rate < 80%.
Hornung 1998a	Patients initially randomized into treatment groups. However, these groups were re-arranged (not randomly) for the purposes of analysis.
Hovell 2003	No outcomes measured.
Insull 2001	Confounded comparison groups.
Jameson 1995	Confounded intervention group (combined adherence intervention with adjustments to medications).
Johnson 1997	Study too short duration.
Johnson 2006	No endpoints reported.
Jones 2003	10 weeks of follow-up.
Kakuda 2001	No intervention intended to affect adherence with prescribed, self-administered medications.
Kardas 2001	Confounded comparison groups.
Katelaris 2002	Confounded comparison groups.
Katon 2002	Confounded comparison groups.
Katon 2004	Measured adherence outcomes but no results reported Unclear whether all patients were on a medication (some took insulin and some had antidepressants).
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.
Kiarie 2003	Confounded comparison groups.
Klein 2001	No measure of adherence.
Kogos Jr. 2004	Not randomized.

	Patients are prescribed medication for a chronic condition but does not specify the medical disorder (might be a range). Unknown follow-up status. Follow-up too short.
Krein 2004	Confounded comparison groups.
Krudsood 2002	No measure of medication adherence.
Kumar 2002	Confounded comparison groups.
Kutcher 2002	Follow-up less than 80% of participants.
Lafeuillade 2001	No intervention intended to affect adherence with prescribed, self-administered medications.
Laffel 2003	No measure of adherence.
Lam 2003	Intervention was 12 to 18 sessions of cognitive therapy, which is a confounder.
Laramee 2003	Confounded comparison groups.
Lawson 2005	Intervention not tailored to improve adherence, only to adjust insulin levels.
Leal 2004	No measurement of adherence.
Lee 2003	No intervention intended to affect adherence with prescribed, self-administered medications.
Leenan 1997	Study too short duration.
Lemstra 2002	No intervention intended to affect adherence with prescribed, self-administered medications.
Leung 2003	Different meds in the 2 arms (rifamp+pyraz versus IHN) as well as different durations (2 months versus 6 months).
Levesque 1983	Confounded comparison groups.
Levine 1979	Missing data on adherence.
Levy 2004	Follow-up too short. Follow-up rate < 80%.
Lewis 1984	Follow-up too short or on less than 80% of participants.
Lin 2003	No measure of treatment outcome.
Linkewich 1974	Missing description of disease outcome.
Linszen 1996	Follow-up too short or on less than 80% of participants.
Logan 1979	Confounded comparison groups.
Lopez-Vina 2000	Follow-up less than 80%.
Lwilla 2003	Follow-up less than 80%.
MacIntyre 2003	No measure of treatment outcome.
Maiman 1978	Missing description of disease outcome.
Malotte 2001	No measure of treatment outcome.
Manders 2001	Follow-up too short or on less than 80% of participants.
Mann 2001	No measure of treatment outcome.
Mannheimer 2002	No intervention intended to affect adherence with prescribed, self-administered medications.
Mannheimer 2006	Follow-up rate < 80%.
Mantzaris 2002	Confounded comparison groups.
MarquezContreras04b	Follow-up rate < 80%.
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, cannot separate effects of the education from the effects of having different physicians.
Maspero 2001	Confounded comparison groups.

Matsuyama 1993	Follow-up too short or on less than 80% of participants.
Maxwell 2002	No intervention intended to affect adherence with prescribed, self-administered medications.
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.
Miklowitz 2003	Less than 80% follow-up.
Millard 2003	No measure of medication adherence.
Miller 1990	Follow-up too short or on less than 80% of participants.
Mita 2003	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.
Morisky 2001	No measure of treatment outcome.
Moulding 2002	No measure of treatment outcome.
Moya 2006	Follow-up rate < 80%. Not an RCT.
Muhlig 2001	No measure of treatment outcome.
Mundt 2001	Less than 80% follow-up at 6 months.
Murphy 2002	No measure of treatment outcome.
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.
Naunton 2003	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.
Noonan 2001	Confounded comparison groups.
Nyomba 2004	76% follow-up rate.
O'Connor 1996	Non-randomised trial.
O'Suilleabhain 2002	Follow-up too short or on less than 80% of participants.
Onyirimba 2003	Follow-up was less than 80%.
Phan 1995	Follow-up too short or on less than 80% of participants.
Polonsky 2003	Follow-up was less than 80%.
Ponnusankar 2004	No measurement of treatment outcome.
Poplawska 2004	No measurement of adherence.
Portilla 2003	Follow-up was less than 80%.
Purcell 2004	No measure of treatment outcome. Not all participants taking medication.
Putnam 1994	Follow-up too short or on less than 80% of participants.
Qazi 2002	No intervention intended to affect adherence with prescribed, self-administered medications.

Rapoff 2002	Follow-up less than 80% of participants.
Rathbun 2005	Follow-up rate < 80%.
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.
Reid 2005	Addiction study (alcoholism).
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.
Rickheim 2002a	No measure of medication adherence.
Rickheim 2002b	No measure of medication adherence.
Rigsby 2000	Follow up less than 6 months, and trial is not definitively negative since there are less than 50 patients per group.
Riis 2001	Confounded comparison groups.
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.
Rodriguez 2003	No intervention intended to affect adherence with prescribed, self-administered medications.
Rosen 2004	Follow-up time was only 4 months.
Ross 2004	78.5% follow-up rate.
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.
Rudnicka 2003	Confounded comparison groups.
Ruoff 2005	Follow-up rate < 80%. No control group. Follow-up too short.
Safren 2003	Follow-up too short or on less than 80% of participants.
Sanchez 2002	Confounded comparison groups.
Sanmarti 1993	Missing description of disease outcome.
Saunders 1991	Follow-up too short or on less than 80% of participants.
Sawicki 1999	Confounded comparison groups.
Schmaling 2001	Follow-up less than 80% of participants.
Schoenbaum 2001	No measure of medication adherence.
Schousboe 2005	No clear measure of treatment outcome.
Schwartz 1981	Confounded comparison groups.
Sclar 1991	Missing description of disease outcome.
Seal 2003	No intervention intended to affect adherence with prescribed, self-administered medications.
Segador 2005	Follow-up rate < 80%.
Seggev 1998	Less than 80% follow-up (78.8%).
Sellors 1997	No treatment outcome measured.
Sellwood 2001	Confounded comparison groups.
Serfaty 2002	No measure of treatment outcome.
Serfaty 2003	Confounded comparison groups.

Shames 2004	Confounded comparison groups.
Sharpe 1974	Missing description of disease outcome.
Shepard 1979	Missing data on adherence.
Sherbourne 2001	No measure of medication adherence.
Sherman 2001	Confounded comparison groups, and no intervention intended to affect adherence with prescribed, self-administered medications.
Shetty 1997	No random assignment to treatment groups.
Silverman 2002	No measure of medication adherence.
Simkins 1986	Missing description of disease outcome.
Simmons 2001	Follow-up too short or on less than 80% of participants.
Simon 2002	No measure of medication adherence.
Simon 2005	Intervention aimed at changing prescribing behaviour. No measure of adherence. Follow-up rate < 80%.
Simon 2006	Follow-up rate < 80%.
Smith 1986	Missing description of disease outcome.
Smith 2003	Follow-up too short or on less than 80% of participants.
Solomon 1988	Missing description of disease outcome. Follow-up too short or on less than 80% of participants.
Solomon 1997	Study too short duration.
Stringer 2003	No measure of treatment outcome.
Stuart 2003	No measure of treatment outcome.
Sturgess 2003	Follow-up too short or on less than 80% of participants.
Stuurman-Bieze 2005	Follow-up too short. No data on control group. No measure of treatment outcome.
Suppapitiporn 2005	No measure of adherence outcome. Unknown follow-up status.
Surwit 2002	No measure of medication adherence.
Svoren 2003	No measure of medication adherence.
Swartz 2001	No measure of treatment outcome.
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.
Taylor 2001	Follow-up too short or on less than 80% of participants.
Taylor 2003	The interventions are mainly directed at enhancing therapy though reviewing patients' drug regimens. Enhancing adherence is a secondary objective; for the outcomes measured, the independent effects of the adherence part can't be separated out.
Tinkelman 1980	Confounded comparison groups.
Toyota 2003	Follow-up too short or on less than 80% of participants.
Treiber 2002	Confounded comparison groups.
Trienekens 1993	Confounded comparison groups.
Unutzer 2001	No measure of treatment outcome.
Unutzer 2002	No intervention intended to affect adherence with prescribed, self-administered medications.

Vale 2003	No measure of medication adherence.
Valles 2003	No measure of medication adherence.
Van Dyke 2002	Confounded comparison groups and no intervention intended to affect adherence with prescribed, self-administered medications.
Van der 2001	No measure of treatment outcome.
Vander Stichele 1992	Follow-up too short or on less than 80% of participants.
Velasco 2002	No measure of medication adherence.
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.
Vivian 2002	Confounded: the intervention included both changing medications as needed and compliance counselling.
Vrijens 1997	Study duration too short.
Wagner 2002	No measure of treatment outcome.
Walker 2006	Confounded comparison groups. No specific disease/disorder being treated. Inadequate measure of clinical outcome.
Wasilewski 2000	Confounded: different medications and different medication schedule in intervention and control groups.
Webb 1980	Confounded comparison groups.
Weiss 2002	Follow-up rate less than 80% of participants.
Wells 2004	Confounded comparison groups.
Williams 1986	Missing description of disease outcome.
Williams 2006	Follow-up rate < 80%.
Windsor 1990	Missing description of disease outcome.
Wise 1986	Follow-up too short or on less than 80% of participants.
Wohl 2006	Follow-up rate < 80%.
Wong 1987	Missing description of disease outcome.
Wright 2003	No measure of medication adherence.
Wu 2006	Follow-up rate < 80%.
Xiang 1994	Follow-up too short or on less than 80% of participants.
Xiao 2001	No intervention intended to affect adherence with prescribed, self-administered medications.
Yeboah-Antwi 2001	No measure of medication adherence.
Yuan 2003	No measure of medication adherence.
Zarnke 1997	Study too short duration.
Zermansky 2002	Patients are not prescribed medication for a medical (including psychological) disorder.
Ziauddin Hyder 2002	No measure of treatment outcome.
de Klerk 2001	No measure of treatment outcome.
de Lusignan 2001	No measure of medication adherence.
de Wit 2001	Follow-up too short (8 weeks).
van Es 2001	No measure of treatment outcome.

Characteristics of excluded studies (*Continued*)

Characteristics of ongoing studies

Study	**Bosworth 2005**
Trial name or title	The veterans' study to improve the control of hypertension (V-STITCH): design and methodology
Participants	588 patients with a diagnosis of hypertension, enrolled in the Durham VAMC primary care clinic and had a filled prescription for a hypertension medication in the past year
Interventions	A cluster-randomized trial with 30 primary care providers randomized to receive the provider intervention or usual care. The provider intervention is a patient-specific electronically generated hypertension decision support system (DSS). For these providers, a sample of their hypertensive patients was randomly assigned to the intervention or usual care. The patient intervention incorporates patients' need assessments and involves tailored behavioral and education modules to promote medication adherence and improve specific health behaviors. All modules are delivered by a nurse case manager over the telephone bi-monthly for 24 months.
Outcomes	The primary outcome is BP control measured at each primary care visit and is obtained from patients' medical records. The secondary outcomes are knowledge and perceived risks associated with hypertension, ability to continue hypertension regimen and medication adherence, which is assessed from pharmacy records for the entire 24-month period
Starting date	Unknown
Contact information	Hayden B. Bosworth, Ph.D; Center for Health Services Research in Primary Care, Duke University, 2424 Erwin Road, Hock Plaza, Durham, NC 27703; 919- 286- 6936; hboswort@acpub.duke.edu
Notes	

Study	**Bosworth 2007**
Trial name or title	The Take Control of Your Blood pressure (TCYB) study: Study design and methodology
Participants	569 patients with a diagnosis of hypertension, using a hypertension medication and enrolled in one of two primary care clinics for at least a year
Interventions	A randomized controlled health services intervention trial with a two by two design testing 1) home blood pressure self-monitoring, and 2) tailored behavioral self-management intervention that is administered via telephone by a nurse
Outcomes	The primary outcome is BP control at baseline and at subsequent 6-month intervals. The secondary outcomes are knowledge and perceived risks associated with hypertension, ability to continue hypertension regimen and medication adherence, which is assessed using self-reported measures
Starting date	Unknown
Contact information	Hayden B. Bosworth, Ph.D; Center for Health Services Research in Primary Care, Duke University, 2424 Erwin Road, Hock Plaza, Durham, NC 27703; 919- 286- 6936; hboswort@acpub.duke.edu
Notes	

Study	**Ogedegbe 2007**
Trial name or title	An RCT of the effect of motivational interviewing on medication adherence in hypertensive African Americans: rationale and design
Participants	190 African American adults, diagnosed with hypertension, taking at least one antihypertensive medication and fluent in English
Interventions	Randomized control trial testing an intervention that uses motivational interviewing techniques to counsel patients about medication adherence and its related behaviors; conducted with the aid of an adapted version of a standardized structured adherence counseling script

Characteristics of ongoing studies (*Continued*)

Outcomes	The primary outcome of medication adherence is accessed via both the MEMS and the Morisky self-report medication adherence questionnaire. Secondary outcomes are within-patient changes in both SBP and DBP, and within-patient changes in self efficacy and intrinsic motivation scores from baseline to 12 months
Starting date	Baseline assessments were completed between July 2002 and May 2005; interventions started in October 2002 and it is ongoing. The 12-month follow-up visits started in July 2003 and are also ongoing
Contact information	Gbenga Ogedegbe, M.D., M.P.H., M.S; Columbia University Medical Center, United States; goo1@columbia.edu
Notes	

ANALYSES

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 as Topic; Randomized Controlled Trials as Topic; Self Administration

MeSH check words

Humans

COVER SHEET

Title	Interventions for enhancing medication adherence
Authors	Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X
Contribution of author(s)	2007 update: RBH - oversight and involvement in all stages of the 2007 review and data extraction for eligible studies. EA - involved in all stages of the 2007 update. HPM - involved in all stages of review for the 2002 update. NS – Involved in reviewing and abstracting articles and some aspects of text preparation for 2007 update. XY - involved in all stages of the 2005 update. Previous versions of the review: Aqeel Degani - involved in searches up to 2003, reviewing articles for eligibility. Patricia Montague - involved in all stages of review for the 1998 update. Amit X. Garg - involved in reviewing references from literature searches for relevance and for calculating agreement statistics for the 2002 and 2005 updates. Sunil Kripalani - involved in reviewing articles for eligibility for 2005 update.
Issue protocol first published	/
Review first published	1999/3
Date of most recent amendment	18 February 2008
Date of most recent SUBSTANTIVE amendment	15 February 2008

What's New	Twenty-one new studies have been added in the 2007 update (published on issue 2 2008 of The Cochrane Library), bringing to 78 the number of randomized trials meeting our criteria for testing interventions to help patients to follow prescribed, self-administered medications. Despite the new studies, our 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 counseling, reminders, self-monitoring, feedback, family therapy, psychological therapy, manual telephone follow-up, and supportive care. For short-term treatments, high adherence can be achieved by simpler means, including counseling, written information about the importance of taking all doses, and personal phone calls.
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	14 September 2007
Date authors' conclusions section amended	14 September 2007
Contact address	Prof R. Brian Haynes Chair Clinical Epidemiology & Biostatistics and Medicine McMaster University Faculty of Health Sciences 1200 Main Street West, Rm. 2C10B Hamilton Ontario L8N 3Z5 CANADA E-mail: bhaynes@mcmaster.ca Tel: +1 905 5259140 Fax: +1 905 5770017
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Analysis 01.01. Comparison 01 Studies that met criteria, Outcome 01 Adherence and Outcome

Adherence and Outcome

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
Al-Eidan 2002	Helicobacter pylori	Intervention patients (n = 38) received their medicines via the hospital pharmacy and were counselled (and followed up) by a hospital pharmacist.	Control patients (n = 38) were given a standard advice sheet and referred to their GP who prescribed the same therapy.	Yes for improving compliance to a 1-week course of triple therapy to eradicate H-pylori.	Yes for improving clinical outcomes for the intervention group who had a significantly higher rate of H-pylori eradication.
Andrade 2005	HIV	Disease Management Assistant System (DMAS) device, programmed with verbal reminder messages and dosing times for medications in the highly active antiretroviral treatment (HAART) regimen with monthly adherence counseling and feedback (see Control; n = 29).	Monthly adherence counseling (education about barriers to adherence, hazards of non-adherence, their prescribed HAART regimen) and adherence feedback (n = 29).	No for all adherence outcomes.	No for CD4+ cell count. Yes for plasma HIV RNA (significant for 2 of 4 measures).
Ansah 2001	Malaria	The use of pre-packed chloroquine tablets (n = 155).	The use of chloroquine syrup (n = 144).	Yes. The tablet form of medicine resulted in higher adherence rates, but it isn't established whether this is due to the formulation or the lack of provision of a standard measuring device.	No, there was no difference in the clinical outcomes.
Bailey 1990	Asthma	Pamphlet, workbook, counselling, phone follow-up, support group, and reinforcement of adherence (n = 132).	Instructional pamphlet alone (n = 135).	Yes.	Yes.
Bailey 1999	Asthma	Two intervention groups: 1) Asthma Self Management Program (n = 78) - a	Usual education from their physician, as well as a standardized set of	No (medication adherence and inhaler use)	No for all clinical outcomes (asthma symptoms, respiratory illness,

Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
		skill-oriented self-help workbook, which patients were counseled about in a one-on-one session and during two asthma support group meetings. Patients were also given peak flow meters and trained to use them for early detection of impending asthma attacks They also received 2 telephone calls and a follow-up letter at 1, 2, and 4 weeks, after the counseling session. 2) Core-Elements Program (n = 76) - a revised, shortened workbook that was reviewed in a 15 to 20 minutes one-to-one counseling session. Patients were trained to use inhalers and peak flow meters. They also received a follow-up telephone counseling session a week later and a follow-up letter two weeks later.	pamphlets containing information about asthma. No steps were taken to ensure that patients read the pamphlets (n = 78).		functional impairment, use of health services.
Baird 1984	Hypertension	Once daily metoprolol (n = 196).	Twice daily metoprolol (n = 193).	Yes.	No.
Beaucage 2006	Acute Infections	Pharmacist telephone follow-up intervention (PTFI; n = 126).	Usual pharmacist intervention (UPI; n = 129).	No.	No for all clinical outcomes.
Becker 1986	Hypertension	Special “reminder” pill	Separate vials for each	No.	No.

Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
		packaging (n = 86).	medication (n = 85).		
Berrien 2004	HIV	The intervention in intervention group (n = 20) consisted of eight structured home visits over a 3-month period by the same home care experienced registered nurse. The visits were designed to improve knowledge and understanding of HIV infection, to identify and resolve real and potential barriers to medication adherence, and ultimately to improve adherence. Spanish-speaking case managers, incentives, notebooks with stickers and pill-swallowing training were also part of the home visit training sessions.	In the clinic setting for control group (n = 17), the physician, nurse and social worker provided standard medication adherence education at clinic appointments generally scheduled at 3-month intervals. Phone follow-ups and a single home visit were planned if the staff felt they were needed. Visual aids for remembering medications, medication boxes, beepers, and general technical and emotional support were regularly offered. The clinic nurse contacted the family by telephone when the patient was starting a new medication, was having difficulty with adherence, or needed clarification and support. A single home visit was planned when and if the clinic staff believed medication adherence was poor despite the implementation of the above listed techniques.	Yes for pharmacy report of refill frequency; no for self-reported.	No.
Brown 1997a	Hyperlipidemia and coronary artery disease	Controlled release niacin twice daily (n = 31).	Regular niacin four times a day (n = 31).	Yes.	Yes.
Brus 1998	Rheumatoid Arthritis (RA)	Six patient education meetings. The education	The control group received a brochure	No.	No.

Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
		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).	on RA, as provided by the Dutch League against Rheumatism. This brochure gives comprehensive information on medication, physical and occupational therapy (n = 31).		
Canto De Cetina 2001	Contraception	175 received detailed structured pretreatment counseling about the hormonal effects of the injectable contraceptive depot-medroxyprogesterone acetate (Depo-Provera).	175 received routine counseling on duration of use and efficacy of the contraceptive method.	Yes for the cumulative termination rates.	Yes for the cumulative termination rates.
Chaplin 1998	Schizophrenia	Individual semi-structured educational sessions discussing the benefits and adverse effects of antipsychotic drugs, including tardive dyskinesia (n = 28).	Usual care (n = 28).	No.	No.

Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
Colcher 1972	Strep throat	Special counselling and written instructions on need to take all pills (n = 100).	Usual care (n = 100).	Yes.	Yes.
Collier 2005	HIV	Serial, scripted and supportive telephone calls from a nurse plus usual adherence support (same as control group; n = 142).	Usual support measures including in-person counselling by a nurse at start of therapy and discretionary phone calls (n = 140).	No.	No.
Cote 1997	Asthma	Extensive asthma education program plus written self-managed action plan based on peak expiratory flow (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.
Cote 2001	Asthma	Patients in Group Limited Education (LE) (n = 30) were given a self-action plan that was explained by the on call physician. The action plan used "traffic lights" (green, yellow, red) to describe specific states of asthma control based on Peak Expiratory Flow and symptoms and actions that the patient should take for each state. Subjects were all instructed by a respiratory therapist or study nurse in the proper use of an inhaler. In addition to what patients in Group LE received,	The patients in Group C (control, n = 35) received the usual treatment given for an acute asthma exacerbation.	No.	No.

Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
		the patients in Group Structured Education (SE n = 33) participated in a structured asthma educational program based on the PRECEDE model of health education within 2 weeks after their randomization.			
Coull 2004	Ischaemic heart disease	Intervention consisted of participation in a mentor-led group (n = 165), through attending monthly 2 hour long meetings in community facilities over a 1-year period. There was an average of 10 patients per group, each led by two mentors. The core activities covered in the programme were lifestyle risk factors of smoking, diet and exercise; blood pressure and cholesterol; understanding of and ability to cope with IHD; and drug concordance. Each mentored group was also encouraged to develop its own agenda. Input was provided from a pharmacist, cardiac rehabilitation specialist nurse, dietician, welfare benefits advisor and	Both intervention and control groups (n = 154) continued to receive standard care.	Yes.	No.

Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
		Recreation Services. Volunteer lay health mentors, aged 54 to 74 recruited from the local community led the groups.			
Ellis 2005	Adolescents with type 1 Diabetes	Standard medical care plus Multisystematic Therapy (MST), an intensive, family-centered, community-based psychotherapy treatment with tailored treatment goals and interventions for each family to best treat the adherence problem. MST interventions targeted adherence-related problems within the family system, peer network, and the broader community systems within which the family was embedded (n = 64).	Standard medical care at a hospital-based endocrine clinic where adolescents were cared for consisted of quarterly medical visits with a multidisciplinary medical team composed of an endocrinologist, nurse, dietician, social worker, and psychologist (n = 63).	No.	No for all clinical outcomes.
Farber 2004	Asthma	Subjects in the intervention group (n = 28) received basic asthma education; instructions on use of a metered-dose inhaler with holding chamber; a written asthma self-management plan illustrated by zones colored green, yellow, and red; a sample age-appropriate holding chamber; and prescriptions	The control group (n = 28) received routine care.	Yes (based on dispensing).	No.

Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
		for medication needed to implement the plan. This medication included an inhaled corticosteroid drug for everyday use and a quick-acting bronchodilator for use as needed. The importance of seeking urgent medical care in the red zone was emphasized. Three brief followup phone calls were placed to patients in the intervention group at 1 to 2 weeks, 4 to 6 weeks and 3 months after enrollment.			
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 1999	Asthma or chronic obstructive pulmonary disease (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,	Usual care from GP (n = 39 asthmatics, n = 32 COPD patients).	No.	No.

Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
		treatment plans, and physiotherapy. One or two 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 weeks of peak flow monitoring (n = 39 asthmatics, n = 32 COPD patients).			
Gani 2001	Seasonal rhinitis and asthma	B group (n = 35) with drug therapy plus training on the use of nasal spray, and C group (n = 36) the same as B plus a lesson on rhinitis and asthma.	A group (n = 30) with drug therapy alone.	Yes for A versus B+C	Yes: between group A and group C in respiratory symptoms. Yes, in the use of inhaled albuterol (Fisher test) among the groups was observed (A versus B plus C: P = 0.005; A versus C: P = 0.005).
Ginde 2003	Macrolide antibiotic treatment	Patients in the ED group (n = 38) were provided a full course of azithromycin (6 X 250 mg) at no charge and given instructions on the proper dose and frequency before discharge from the ED.	Patients in the pharmacy group (n = 36) received a written prescription for a full course of azithromycin before discharge from the ED.	No.	No. The prescription filling rate for the control group is based on the assumption that control patients used a participating pharmacy 8 blocks away that provided the drugs free of charge - patients were apparently not asked if they filled their prescription elsewhere. The "course completed" rate is based on self report on a telephone

Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
					call - no indication that interviewers were blinded to group; nor was the exact question given (if there was one). Technically, this study qualified for the review, but the reliability and credibility of the measures are suspect. At least the question of the control group's filling of prescriptions could have been cleared up. The intervention is also impractical in any setting where giving drugs out for free isn't possible.
Girvin 1999	Hypertension	Enalapril 20mg once daily (n = 27). Cross-over study, with 4 week study periods.	Enalapril 10mg twice daily (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.
Hederos 2005	Children with asthma	Group meetings (weekly X 3, then 6 months later, 1.5 hours each) for parents of children with asthma held by a multidisciplinary team (paediatrician, nurse, psychologist) + usual care and basic education (see Control group strategy; n =	Family received education about asthma at the first visit to the clinic. They received a written treatment plan that tailored the lowest effective dose. Treatment was stopped if the child had no asthma for 6 months (n = 28).	Yes for parents and doctors estimated adherence on a visual analogue scale (VAS), for poor adherence and for greater than or equal to 100% adherence. No for estimated adherence tracked from diaries, for good adherence, and for	No for all clinical outcomes.

Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
		32).		verified adherence from measured doses	
Henry 1999	H. Pylori infection	10 days of omeprazole 20mg twice daily, amoxicillin 500mg three times a day and metronidazole 400 mg three times a day, 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 encouraged by a phone call 2 days after the start of therapy (n = 60).	10 days of omeprazole 20mg twice daily, amoxicillin 500mg three times a day and metronidazole 400 mg three times a day, verbal advice on medication use and its possible side effects in an initial 20 minute consultation (n = 59).	No.	No.
Hill 2001	Rheumatoid arthritis	The intervention group (n = 51) received 7 x 30 minute one to one sessions of patient education.	The control group (n = 49) received standard management.	Yes for improving adherence to D-penicillamine (DPA) for rheumatoid arthritis.	No for improving clinical outcomes of plasma viscosity, c-reactive protein, articular index, morning stiffness and pain score.
Howe 2005	Children with type 1 diabetes	Two intervention groups, standard care (see Control) plus: 1) Education (ED) - One-time session by the study coordinator that aimed to provide families with basic diabetes	Standard care (SC) from a nurse practitioner and endocrinologist (n = 28).	Yes for the adherence questionnaire (ADH), in comparison between the ED & TCM group versus the SC group.	No for both intervention groups.

Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
		management skills (n = 21). 2) Education and telephone case management group (ED & TCM) -TCM consisted of standardized telephone calls which reviewed blood sugars, safety issues, problem-solving skills, diet and meal planning, and changing insulin dose, as well as parenting and behavior management skills with parents as needed (n = 26).			
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 to 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 to 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

Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
					antipsychotic drug.
Kemp 1998	Psychotic disorders	4 to 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 to 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.
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.
Laporte 2003	Compliance and stability of international normalized ratio (INR) of two oral anticoagulants with different half-lives	The standard education group received the minimum information consistent with ethical oral anticoagulant therapy (OAT) with no particular emphasis on the necessity of strict compliance. Patients in the intensive education group received information about the causes of anticoagulation instability and the importance of strict adherence. The intensive education group were provided information	A 2 by 2 factorial design with patients randomly allocated to warfarin (long half-life, n = 43) or acenocoumarol (short-half life, n = 43) and to either intensive education (n = 43) or standard education (n = 43).	No.	No.

Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
		through visual material, were visited daily by nurses and physicians to repeat some items, and were tested daily about their education. The education, either standard or intensive, was given until hospital discharge.			
Lee 2006	Hypertension & hyperlipidemia	Comprehensive pharmacy care program consisting of 3 elements (n = 83): - Individualized medication education - Medications dispensed using blister packs - follow-ups every 2-months by clinical pharmacists.	Usual care (n = 76; followed a 6 month comprehensive care period; patients were then given 90 day supply or their meds with one repeat).	Yes.	Yes for systolic blood pressure. No for diastolic blood pressure and LDL-C.
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 attacks. Not statistically significant for use of inhaled topical steroids and rescue medication for mild attacks.	Yes.
MarquezContreras04a	Hypercholesterolaemia	The intervention group (IG) of 63 patients received the standard care given to control group, and in addition received a telephone call at 7 to 10 days, 2 months, and 4 months. The goal of	The control group (CG) of 63 patients, who received the doctor's normal treatment, which included oral information about hypercholesterolemia, advice about its control, brochures about dietary	Yes.	Yes for the 6-month decrease in total cholesterol and LDL-C was significantly different between IG and CG (Table 3). No for the 6-month decrease in triglycerides and HDL-C.

Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
		the intervention was to establish the level of compliance, categorize this as adequate or inadequate, and make recommendations based on that. Level of compliance was determined by comparing the number of pills consumed to the number that should have been consumed (calculated using self-reported information about the number of pills remaining, number of pills dispensed, and fill date of the prescription). Compliance was defined as taking 80 to 110% of the pills that should have been taken thus far. Compliant patients were congratulated and encouraged to continue their good level of compliance as it would lower their risk of heart disease. Noncompliant patients were notified their behavior was considered noncompliant and encouraged to better comply with therapy as it would lower their risk of heart disease.	recommendations, 3 month-long prescriptions for a cholesterol-lowering medication, and titration of that medication if indicated at 3 months.		

Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
MarquezContreras2005	Hypertension	Two intervention groups (both receiving routine primary care plus 1 of): 1) Telephone intervention (TIG; n = 216) - Patients received 3 telephone calls (15 days, 2 months, 4 months) by nurse to reinforce compliance and remind them of scheduled visits. The nurse gave feedback about compliance based on patient self-report of pills consumed. 2) Mail intervention (MIG; n = 212) - Patients received 3 mailed communications (15 days, 7 weeks, 15 weeks) to promote compliance through education in hypertension, medication compliance, and reminders of scheduled visits.	Routine primary care for hypertension (n = 212).	Yes for pill count in both intervention groups in comparison to the control group.	Yes for blood pressure control in both the TIG and the MIG in comparison to the control group. Yes for both SBP and DBP at 6 months for both the TIG and the MIG when compared to the control group. Yes for both SBP and DBP reduction from baseline to 6 months in the TIG in comparison to the control group.
MarquezContreras2006	Hypertension	Usual care plus OMRON automatic monitor for home blood pressure monitoring (HBPM), a card to record pressures, with an instruction book and phone call to go over instructions (n = 100).	Usual care in a primary care setting at 40 sites (n = 100).	Yes.	No for all clinical outcomes except the change in diastolic blood pressure from baseline to 6 months between groups.
Merinder 1999	Schizophrenia	8-session psychoeducational	Usual treatment provided in community psychiatry	No.	Yes for knowledge of schizophrenia and for VSSS

Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
		programme for schizophrenic patients and their relatives, conducted using a mainly didactic interactive method (n = 23).	(n = 23).		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).
Morice 2001	Asthma	Subsequent visits from the asthma nurse until discharge from hospital (n = 35).	'Routine care' from medical and nursing staff but no further intervention from the asthma nurse (n = 30).	No (on the contrary, medication compliance of ß-agonist inhaler in intervention group was lower than in control group).	No for the total occasions of GP call-out and re-admission. Yes for patients percentage of claiming to have a writing management plan and self-management.
Nazareth 2001	Complex regimens in the elderly (aged 75 years and older on four or more medicines who had been discharged)	The hospital pharmacist developed discharge plans which gave details of medication and support required by the patient. A copy was given to the patient and to all relevant professionals and carers. This was followed by a domiciliary assessment by a community pharmacist. (n = 165).	In the control group, patients were discharged from hospital following standard procedures that included a discharge letter to the general practitioner listing current medications (n = 151).	No.	No.
O'Donnell 2003	Schizophrenia	The experimental group (n = 28) received 5 sessions of compliance therapy, each session lasting 30 to 60 minutes. The sessions covered a review of the patient's illness history,	The control group (n = 28) received non-specific counseling comprising of 5 sessions lasting 30 to 60 minutes.	No.	No.

Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
		understanding of the illness and his or her ambivalence to treatment, maintenance medication and stigma. Compliance therapy is a cognitive behaviour intervention with techniques adapted from motivational interviewing, other cognitive therapies and psychoeducation.			
Odegard 2005	Poorly controlled Type 2 diabetes, on oral meds	Usual care (see Control) plus: Pharmacist-led intervention (n = 43): - Pharmacist-patient communication on diabetes progress - Pharmacist-provider communication on the subject's progress - Medication-related problems - the pharmacists were not formally affiliated with the clinic.	Usual care (primary care, university-based, medical clinics; n = 34).	No.	No for all clinical outcomes.
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.
Peterson 2004	Dyslipidemia	Patients in the intervention group (n = 45) were visited at home monthly by a pharmacist, who educated the patients	Patients in the control group (n = 49) received standard medical care. There was no further contact with patients in	No.	No.

Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
		on the goals of lipid-lowering treatment and the importance of lifestyle issues in dyslipidaemia and compliance with therapy, assessed patients for drug-related problems, and measured total blood cholesterol levels using point-of-care testing.	the control group after the initial collection of baseline data, until 6 months had lapsed. At that time, their final total blood cholesterol level was measured, and the current medication regimen and self-reported compliance were recorded.		
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.
Portsmouth 2005	HIV	Participants were assigned to take Stavudine (d4T) which is a prolonged-release once-daily formulation of a thymidine-based nucleoside reverse transcriptase inhibitor (NRTI). Both groups continued their other meds (n = 22).	Participants in the control group were assigned to continue the twice daily version of d4T (IR/3TC/EFV or Combivirs/EFV) as per their screening regimen (n = 21).	No for all adherence outcomes.	No for all clinical outcomes.
Pradier 2003	HIV	Patients (n = 100) in the intervention group (IG) were offered three individual sessions by trained nurses.	No mention was made of the care that was provided for the control group (n = 102).	Yes	No. The clinical significance of these findings is unclear - adherence rate was on self-report in an unblinded trial,

Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
					the mean HIV RNA was no different at 6 months for the 2 groups and no actual clinical outcomes were reported.
Ran 2003	Schizophrenia	Family education sessions monthly (FIG, n = 127). A second group received meds only (MG, n = 105).	Usual care (CG, n = 115).	Yes for FIG versus both other groups	Yes for relapse rate for FIG versus other groups. FIG and MG both better than control for symptoms.
Rawlings 2003	HIV	4 modules of the Tools for Health and Empowerment HIV education intervention (EI) plus routine counseling (RC) (EI + RC; n = 96)	Routine counseling alone (RC; n = 99).	No.	No.
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).
Remien 2005	HIV	Usual care (see Control) plus a four-session (45 to 60 minutes each, over 5 weeks), couple-focused adherence intervention consisting of treatment and adherence education, identifying adherence barriers, developing communication and problem-solving strategies,	Usual care from a multidisciplinary treatment team, including monthly visits with provider if nonadherent (n = 109).	No.	No for all clinical outcomes.

Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
		optimizing partner support, and building confidence for optimal adherence, with each partner receiving $20 for each session attended (n = 106).			
Rickles 2005	Depression	Usual care (see Control) plus: Pharmacist-guided education and monitoring (PGEM) -to address concerns, educate, and help patients increase adherence to medication (n = 31).	Usual Care - no special counselling or monitoring of adherence (n = 32).	No for all adherence outcomes.	No.
Rudd 2004	Hypertension	A nurse care manager conducted baseline counselling on the correct use of the automated blood pressure (BP) device, regular return of the automatically printed BP reports, tips for enhancing adherence, and recognition of drug side effects; the nurse phoned patients at 1 week, 1, 2, and 4 months. The nurse changed doses on own and called physician for medication changes (n = 74).	Usual care (n = 76).	Yes.	Yes for changes in both systolic and diastolic blood pressure from baseline to 6 months between groups.
Sackett 1975	Hypertension	(a). Care at worksite by occupational health physicians (n = 37) (b). Detailed 'programmed' instructions about	Neither intervention (n = 25)* * numbers provided by author.	No.	No.

Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
		hypertention and adherence (n = 28) (c). Both a and b (n = 44).			
Sadik 2005	Heart failure	Usual care plus: Booklets and education on heart failure (HF) and training on a self-monitoring programme (daily weights and symptom diary, to share with physician and pharmacist; extra dose of diuretic if weight rose). Research pharmacist interacted with physicians to simplify drug regimens, with patients on follow-up visits to clinic (n = 109).	Usual care in a medical or cardiology clinic (n = 112).	Yes.	Yes for 2-minute walk test, blood pressure and pulse, HF symptoms, forced vital capacity and both quality of life measures - the MLHFQ and SF36.
Samet 2005	HIV	Usual medical care plus Nurse-led intervention (60 minute session + 3 follow-up visits) with 4 parts (n = 74): a) Assessment of the alcohol and substance use b) A watch to time medications and improve adherence c) Enhancement of perceived efficacy of medications d) Individualized HIV counselling.	Patients received regular medical care for HIV infection. This included verbal or written instructions about optimal medication strategies (n = 77).	Yes.	No for all clinical outcomes.
Schaffer 2004	Asthma	(a). Audiotape alone (n = 10) (b). National Heart Lung and Blood Institute (NHLBI) booklet alone (n	Standard provider education (control) (n = 13).	Yes for positive effect on adherence by pharmacy-refill measure for booklet versus control, and for	No.

Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
		= 12) (c). Audiotape plus NHLBI booklet (n = 11).		booklet + audiotape versus control, but not for audiotape versus control, at 6 months. No for self-reported adherence.	
Schroeder 2005	Hypertension	Usual care (see Control) plus nurse-led adherence support sessions (20 minutes initially, 10 minutes 2 months later) with the following goals (n = 128): - Patients address problems with blood pressure lowering medication - Explain diagnosis and the treatment process - Address patient concerns with their medication and tailor strategies to resolve any problems.	Usual care at their doctors' practices, other than blood pressure checks at similar intervals as the intervention group (n = 117).	No for all adherence outcomes.	No for all clinical outcomes.
Stevens 2002	Helicobacter pylori	A longer adherence counseling session and a follow-up phone call from the pharmacist during drug treatment (n = 163). All subjects were given the same 7-day course of omeprazole, bismuth subsalicylate, metronidazole, and tetracycline hydrochloride (OBMT).	A standard antibiotic regimen and randomly assigned to receive usual-care counseling from a pharmacist (n = 162). All subjects were given the same 7-day course of omeprazole, bismuth subsalicylate, metronidazole, and tetracycline hydrochloride (OBMT).	No.	No. (The big problems with this study are that a) both groups got blister packs with daily doses clearly marked; b) both groups got counseling, although this was longer and more detailed for the IC than CG; c) self-report was used for measuring adherence (insensitive). All these factors would bias towards no difference.)

Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
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 highly active antiretroviral treatment (HAART) (i.e. forgetting, side effects, changes in daily routine). Phone number was given should patients have any questions before next interview. Verbal reinforcement of adherence at follow-up visits (n = 55).	Usual medical follow-up (n = 61)	No.	No.
Van Servellen 2005	HIV	Usual care + nurse practitioner and health educators provided modular instruction to patients (5 sessions) to: - Increase patients' HIV knowledge - Increase communication with medical staff - Address patients' unique actual or potential risks for non-adherence The NP followed	Usual care (n = 43).	No for all adherence outcomes.	No for CD4 count, HIV-RNA viral load, and health status and disease progression from self-reports and medical charts.

Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
		up with phone or face-to-face case-management sessions (n = 42).			
Vergouwen 2005	Depression	Depression Care Programme (n = 81) targeted both patients and their GPs- Participants received a newsletter with information about depression, the need to continue antidepressant medication for 6 months, and the importance of social support, and had homework assignments. Their GPs received newsletter summaries and copies of the homework and were to use motivational interviewing with patients.	Patients and doctors did not have the program, but patient follow-ups were scheduled at the same frequency as for the intervention group, and GPs did the same assessments for depression and compliance (n = 96).	No.	No for all clinical outcomes.
Volume 2001	Ambulatory elderly (> or = 65 years of age)	Pharmacists (in n = 8 pharmacies, 159 patients) used the Pharmacist's Management of Drug-Related Problems (PMDRP) instrument to summarize the information collected during the patient interview and the subjective, objective, assessment, and plan record to document actions and follow-up.	Pharmacists at control pharmacies (n = 8 pharmacies, 204 patients) continued to provide traditional pharmacy care.	No.	No.
Walley 2001	Tuberculosis	170 were assigned DOTS	162 were assigned self-	No.	No.

Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
		with direct observation of treatment by health workers; 165 were assigned DOTS with direct observation of treatment by family members.	administered treatment.		
Weber 2004	Intervention group participants received cognitive behavior therapy in addition to usual care.	Participants were randomly assigned to a psychotherapist and given the contact information to schedule their own first appointment. Protocol defined a minimum of three and a maximum of 25 sessions within the 1-year study period. Participant and psychotherapist determined the frequency of appointments and set their own goals for future interventions. Intervention group participants (n = 32) received cognitive behavior therapy in addition to usual care, while control group participants (n = 28) received usual care alone.	Both intervention and control groups continued to receive standard care. Standard care included monthly visits for 12 months with assessments of clinical and laboratory data, course of treatment, drug adverse events and HIV-1 RNA.	No.	No.
Weinberger 2002	Asthma or chronic obstructive pulmonary disease (COPD)	The pharmaceutical care program (n = 447) provided pharmacists with recent patient-specific clinical data (peak expiratory flow rates (PEFRs), emergency department (ED) visits, hospitalizations, and	The PEFR monitoring control group (n = 363) received a peak flow meter, instructions about its use, and monthly calls to elicit PEFRs. However, PEFR data were not provided to the pharmacist. Patients	Yes, for within-group at 6 and 12 months; no for between-group	Yes. At 12 months, patients receiving pharmaceutical care had significantly higher peak flow rates than the usual care group (P = 0.02) but not than PEFR monitoring controls (P = 0.28). There were no

Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
		medication compliance), training, customized patient educational materials, and resources to facilitate program implementation.	in the usual care group (n = 303) received neither peak flow meters nor instructions in their use; during monthly telephone interviews, PEFR rates were not elicited. Pharmacists in both control groups had a training session but received no components of the pharmaceutical care intervention.		significant between-group differences in HRQOL, but patients participating in our program were significantly more satisfied with their pharmacists than the other two groups.
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 minute interaction among the families), plus $100 monetary incentive	Current Therapy (n = 41) - standard pediatric endocrinology follow-up and self-management training.	No for BFST and ES at posttreatment. Yes for BFST at 6 and 12-months. No for ES at 6 and 12-months.	No for BFST in diabetic control or adjustment to diabetes. Yes for BFST on PARQ scales at posttreatment, 6 and 12 months. No for ES.

Adherence and Outcome (*Continued*)

Study	Clinical Problem	Intervention	Control	Effect on Adherence	Effect on Outcome
		for attending all 10 intervention sessions (n = 40).			
Xiong 1994	Schizophrenia	Family counselling and close follow-up (n = 34).	Prescription of medication without formal follow-up (n = 29).	No.	Yes.
Yopp 2004	Adolescents with type 1 Diabetes	Usual care (see Control) plus Multisystemic Therapy (MST; n = 27) - a home-based psychotherapy, the goal is to understand which factors are maintaining poor health status.	Usual care in a multidisciplinary childrens' endocrinology clinic (n = 26).	No for the Diabetes Management Scale. Yes for the 24-Hour Recall Interview, specifically the insulin adherence.	No.
Zhang 1994	Schizophrenia	Family intervention (n = 42).	Prescription of medication without formal follow-up (n = 41).	No.	Yes.
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.