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Interventions to improve adherence to lipid lowering medication

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Abstract

Background—Lipid lowering drugs are still widely underused, despite compelling evidence about their effectiveness in the treatment and prevention of cardiovascular disease. Poor patient adherence to medication regimen is a major factor in the lack of success in treating hyperlipidaemia. In this review we focus on interventions, which encourage patients at risk of heart disease or stroke to take lipid lowering medication regularly.

Objectives—To assess the effect of interventions aiming at improved adherence to lipid lowering drugs, focusing on measures of adherence and clinical outcomes.

Search strategy—We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PsycInfo and CINAHL. Date of most recent search was in February 2003. No language restrictions were applied.

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CONTRIBUTIONS OF AUTHORS

Angela Schedlbauer obtained funding for the review. Designed, coordinated and wrote the review. Was responsible for data collection and interpreting of the data.

Knut Schroeder conceived the review and was involved with the review design and writing of the protocol. Provided general advice on the review and contributed to the screening of search results, data extraction, interpretation of data. Commented on successive drafts of the manuscript

Tom Fahey was involved with developing the protocol, interpreting the data, commenting on the included studies and successive drafts of the manuscript of the review.

Tim Peters was involved with the analysis of data, provided general advice on interpreting the data and commented on successive drafts of the manuscript.

DECLARATIONS OF INTEREST

None known

NOTES The Peninsula Technology Assessment Group (PenTAG) at Peninsula Medical School, Exeter, UK and the Cochrane Heart Group have been awarded a 3-year grant from the National Institute for Health Research to update existing Cochrane systematic reviews relevant to public health, primary care and rehabilitation.

This review is scheduled to be updated in the first year of the program. Publication of the updated review is anticipated by issue 2, 2009 at the latest.

Selection criteria—Randomised controlled trials of adherence-enhancing interventions to lipid lowering medication in adults for both primary and secondary prevention of cardiovascular disease in an ambulatory setting.

Data collection and analysis—Two reviewers extracted data independently and assessed studies according to criteria outlined by the Cochrane Reviewers' Handbook.

Main results—The eight studies found contained data on 5943 patients. Interventions could be stratified into four categories: 1. simplification of drug regimen, 2. patient information/education, 3. intensified patient care such as reminding and 4. complex behavioural interventions such as group sessions. Change in adherence ranged from –3% to 25% (decrease in adherence by 3% to increase in adherence by 25%). Three studies reported significantly improved adherence through simplification of drug regimen (category 1), improved patient information/education (category 2) and reminding (category 3). The fact that the successful interventions were evenly spread across the categories, does not suggest any advantage of one particular type of intervention. The methodological and analytical quality was generally low and results have to be considered with caution. Combining data was not appropriate due to the substantial heterogeneity between included randomised controlled trials (RCTs).

Authors' conclusions—At this stage, no specific intervention aimed at improving adherence to lipid lowering drugs can be recommended. The lack of a gold standard method of measuring adherence is one major barrier in adherence research. More reliable data might be achieved by newer methods of measurement, more consistency in adherence assessment and longer duration of follow-up. Increased patient-centredness with emphasis on the patient's perspective and shared-decision-making might lead to more conclusive answers when searching for tools to encourage patients to take lipid lowering medication.

Medical Subject Headings (MeSH)

*Patient Compliance; Antilipemic Agents [*therapeutic use]; Cardiovascular Diseases [prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Humans

BACKGROUND

Despite compelling evidence about the effectiveness of lipid lowering drugs and the introduction of clear guidelines in recent years, lipid lowering therapy is still underused. According to a cross-sectional study, target cholesterol concentrations are only achieved in fewer than 50 per cent of people receiving treatment (Primatesta 2000). Lack of adherence and high discontinuation rates have been shown to be important factors in failing treatment when looking at both high cholesterol levels (Maenpaa 1991) and morbidity in terms of recurrent myocardial infarction (Wei 2002).

Hyperlipidaemia is an important risk factor for coronary heart disease and causes about one-third of cardiovascular disease (CVD) worldwide (WHO 2002). Elevated serum

concentrations of total cholesterol (TC), low-density-lipoprotein (LDL) and total triglycerides (TRG) are associated with an increased coronary heart disease (CHD) risk, whereas high-density-lipoproteins (HDL) or a low TC/HDL ratio appear to be protective. Treatment of hyperlipidaemia with lipid lowering medication (hypolipidaemics) include statins, fibrates or anion-exchange resins. Statins in particular have been shown to be effective in preventing CHD events and in reducing overall mortality in large randomised controlled trials (Athyros 2002a; Downs 1998; 4S 1994; MRC/BHF 2002; Sacks 1996; Shepherd 1995; LIPID 1998). Fibrates and anion-exchange resins also achieved reduction in CHD events, but showed a non-significant increase in non-coronary mortality (Downs 1998; SIGN 1999). Statins are therefore recommended as first line therapy, whereas fibrates and anion-exchange resins can be considered as second line therapy, also in combination with statins (Downs 1998; SIGN 1999).

Recommendations about drug treatment vary from country to country. In the UK, treatment with statins is indicated in patients with atherosclerotic disease to reduce further ischaemic events for secondary prevention. For primary prevention, medication is recommended in asymptomatic patients with a total serum-cholesterol of 5 mmol/l (194 mg/dl) or greater, whose risk of developing CHD over 10 years is above 30 per cent (DOH 2000). The aim of current treatment targets is to decrease total serum-cholesterol concentrations to below 5mmol/l or by 20 to 25 per cent, whichever results in the lower concentration (DOH 2000). US guidelines recommend drug treatment to anyone with an LDL over 100mg/dl (2.6mmol/l), whose CHD risk over 10 years is 20 per cent or above (ATP III). A combination of statins, blood pressure lowering drugs and low dose aspirin is recommended by The World Health Report 2002 for secondary prevention of CVD, as this could cut death rates and disability rates from CVD by more than 50 percent (WHO Report 2002). In England, 7000 myocardial infarctions and 2500 strokes could be avoided each year if individuals at high risk, who are not taking medication, received lipid lowering treatment (Primatesta 2000). These figures show the impact of lipid lowering drugs on public health and thus the importance of their acceptance by patients.

Adherence is defined as the extent as to which patients take medication as prescribed. Since the landmark publication by Sacket et al in 1976 (Sackett 1976), it has been the focus of research over the last three decades which was summarised in a review by Vermeire (Vermeire 2001). Adherence can be intentional and non-intentional and is determined by a variety of factors such as lack of knowledge, denial, adverse effects, poor memory, adverse attitudes to treatment and others. Reliable indicators of adherent behaviour have not been found to date and demographic factors such as age, sex or social class have been shown to be poor predictors of adherence (Vermeire 2001). The importance of the patient's agreement (Lewis 2003) and the significance of the patient's role within the doctor-patient relationship have been emphasised (RPS 1997). As a consequence, adherence and concordance have been used in recent years as more patient-centred synonyms for compliance (Mullen 1997). The treatment of hyperlipidaemia, a symptomless condition, aims at reducing CHD risk and has no immediate effect on patients' wellbeing. In addition to adverse effects caused by medical treatment, this might make it particularly hard for patients to stick to a long-term regimen. It has been difficult to identify the scope of the problem, as adherence rates from hyperlipidaemia trials show considerable variation ranging from thirty-seven to eighty per

cent, depending on factors such as study population, background morbidity, classes of drugs, duration of follow-up and adherence measuring methods (Tsuyuki 2001). Epidemiological data show that only one in four patients continued taking lipid lowering medication long-term: Twenty-five per cent of elderly patients maintained good adherence to a statin after five years in a cohort study enrolling 34,501 patients (Benner 2002). Not surprisingly, primary prevention trials appear to have higher discontinuation rates than secondary prevention trials, which indicates a relationship between adherence and awareness of illness (Tsuyuki 2001). This was confirmed in a recent population-based study involving elderly people, where sixty per cent of patients prescribed a statin for acute coronary syndrome gave up treatment within two years, compared to seventy-five per cent without coronary disease (Jackevicius 2002).

Three systematic reviews published in the Cochrane Library looked at adherence-enhancing interventions. Haynes et al presented methods that were effective in improving adherence to prescribed medication. They were mostly complex, including combinations of more convenient care, information, reminders, self-monitoring, reinforcement, counselling, family therapy and other forms of supervision or attention (Haynes 2004). Even the most effective intervention did not lead to large improvements in adherence and treatment outcomes. The review included one study looking at lipid lowering drugs, which reported improved medication adherence by reducing the dosing frequency (Brown 1997). Schroeder and colleagues focused on medication for controlling blood pressure and reported enhanced adherence by reducing the number of daily doses. They suggested innovative approaches to be introduced in the context of further RCTs, considering motivational strategies and complex interventions in particular (Schroeder 2004b). Another review found educational and supportive counselling to be the only available intervention to increase adherence to highly active antiretroviral therapy for HIV/AIDS (Haddad 2000).

In this review, we focus on interventions designed to help people take their lipid lowering medication in an ambulatory care setting.

OBJECTIVES

To determine the effect of adherence-enhancing interventions on adherence to prescribed, self-administered lipid lowering medication and on clinical outcomes.

METHODS

Criteria for considering studies for this review

Types of studies—Randomised controlled trials (RCTs) of parallel group or crossover design, that used individual or cluster randomisation.

Types of participants—All adults (over 18 years of age) who were prescribed lipid lowering medication for primary or secondary prevention of cardiovascular disease in ambulatory care settings.

Types of interventions—Interventions of any type intended to increase adherence to self-administered lipid lowering medication versus ‘usual care’ or ‘no intervention’.

This will include, but is not exclusive to interventions such as:

- (1) Simplification of drug regimen;
- (2) Patient education and information;
- (3) Intensified patient care (increased follow-up, sending out reminders, etc.);
- (4) Complex behavioural approach (increasing motivation by arranging group sessions, giving out rewards, etc.);
- (5) Decision Support Systems;
- (6) Administrative improvements (audit, documentation, computers).

Types of outcome measures—Measuring adherence continues to be widely variable and remains controversial. Four categories of adherence assessment can be identified and have been included:

- (1) Indirect measures of adherence (e.g. pill count, prescription refill rate, electronic monitoring);
- (2) Subjective measures of adherence (e.g. patients’ self-report in diaries, interviews);
- (3) Direct measures of adherence (tracer substances in blood or urine);
- (4) Physiological indicators (e.g. total cholesterol, LDL, HDL, apolipoproteins, triglycerides, and respective ratios);
- (5) Health outcome indications (e.g. quality of life, morbidity, mortality);
- (6) Adverse effects.

In the literature, physiological indicators, health outcomes and adverse effects are used as proxy measures for adherence (see table of excluded studies). Studies are only included if these are reported in association with adherence outcomes.

Search methods for identification of studies

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) on *The Cochrane Library*, MEDLINE, EMBASE, PsycINFO and CINAHL. The search included ongoing trials (e.g. UK National Research Register and Trials Central). All languages were included. Searches were conducted in:

- CENTRAL on Issue 1, 2003 (Table 1);
- MEDLINE (from January 2000 to February 2003);
- EMBASE with an appropriate RCT filter (Lefebvre 1996) from January 1998 to February 2003 (Table 2);
- CINAHL from January 1982 to February 2003 (Table 3);

- PsychINFO from 1972 to February 2003 (Table 4).

CENTRAL incorporates all controlled trials from EMBASE and MEDLINE with exception of the most recent years. To avoid duplicates, the search in these two databases only covered the years in which controlled trials would not have been included in CENTRAL.

In addition, we searched reference lists of retrieved papers and contacted 8 study authors and experts in the field for additional information on further published and unpublished studies.

Specific search terms—The following terms were used to search MEDLINE in February 2003, with the addition of a filter for randomised controlled trials (Dickersin 1994). These were adapted appropriately for other databases (See Table 1, Table 2, Table 3 and Table 4).

1. exp HYPERLIPIDEMIA/
2. exp Antilipemic Agents/
3. hypercholesterol\$.tw.
4. hyperlipid\$.tw.
5. statin\$.tw.
6. antilipid\$.tw.
7. hyperlip?emia.tw.
8. dyslip?emia.tw.
9. lipid lowering.tw.
10. or/1-9
11. exp Patient Compliance/
12. Treatment Refusal/
13. Patient Dropouts/
14. exp Attitude to Health/
15. Patient Satisfaction/
16. (adher\$ or non-adherence\$ or nonadherence\$).tw.
17. (compliance\$ or noncompliance\$ or non-compliance\$).tw.
18. (refusal or refuse\$).tw.
19. (improv\$ adj5 (follow-up or follow up)).tw.
20. (dropout\$ or drop-out\$ or drop out\$).tw.
21. (patient\$ adj3 (attitude\$ or acceptance\$ or satisfaction)).tw.
22. (treatment\$ adj3 (stop\$ or abandon\$)).tw.
23. or/11-22

24. exp Counseling/
25. patient care/
26. Case Management/
27. Health Behavior/
28. exp Patient Education/
29. exp Behavior Therapy/
30. (behavi\$ adj3 (modif\$ or therap\$ or adjust\$)).tw.
31. Patient Care Planning/
32. Nurse Practitioners/
33. Pharmacists/
34. counsel\$.tw.
35. patient education\$.tw.
36. (patient\$ adj3 educat\$).tw.
37. ((nurse\$ or pharmac\$) adj3 (led\$ or manage\$ or program\$ or based)).tw.
38. or/24-37
39. 23 or 38
40. 10 and 39

Data collection and analysis

Study selection—Two reviewers selected studies independently by assessing titles and abstracts. Full text articles of potential relevance were obtained. Following this initial screening, trials were selected by applying predetermined inclusion criteria. A trial was included if it met all our inclusion criteria. Disagreements were discussed and resolved between the reviewers. A reference management system (Reference Manager) was used to identify and extract duplicate studies.

Study evaluation—Quality assessment was performed using the four main sources of systematic bias in trials: selection bias, performance bias, attrition bias and detection bias. Guidelines about quality assessment of the Cochrane Reviewers' Handbook were followed (Alderson 2004). Allocation concealment, blinding to assessment of outcomes, losses to follow up and adequacy of control were coded as adequate (A), unclear (B), inadequate (C) or not used (D). Any disagreements were resolved by discussion involving a third party if necessary. Records were kept in form of a 'Quality of reporting of meta-analyses, or QUOROM, statement (Moher 1999). We also took into consideration the method used to measure adherence, as some methods are more likely to be biased than others (see under study description).

Data extraction—Study outcome data were extracted using pre-defined data collection forms that had been developed for this review. The form was developed and piloted on a random sample of three studies and refined appropriately. Data were extracted by two reviewers independently. We contacted 6 study authors of original studies for clarification of details or further information, of whom 5 responded.

Data analysis—Heterogeneity between studies detected in various areas (adherence measurement, patient characteristics, duration, interventions used) did not allow pooling of the data. We attempted to group studies according to the type of interventions (see below) and to compare the outcomes independently from each other. We also attempted to recalculate outcomes where the reported data allowed this, using the Stata 8.0 statistical software package (Stata).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

The search contained 2380 articles, of which 2292 were excluded by assessing titles and abstracts (no RCT design, not an ambulatory setting, not concerned with lipidaemia, or not concerned with adherence). We retrieved 88 full text articles and excluded 80 trials (3 were not concerned with lipidaemia at all, 37 were not designed as RCTs, 32 did not focus on interventions to improve adherence and 8 did not have adherence as an outcome). 8 studies met all the inclusion criteria and were included in the review, the combined patient number being 5943. The study size varied from 30 to 4548 patients. The trials showed a great variation in type of participants, setting, medication, intervention used and outcomes measured, which are described in more detail in the Characteristics of Included Studies Table.

Interventions—Stratification of interventions into groups was performed on pragmatic grounds as generally accepted categories do not exist. Four main groups were identified:

- (1) Simplification of drug regimen (Brown 1997; Sweeney 1991);
- (2) Patient education and information (Poston 1998; Powell 1995);
- (3) Intensified patient care: Reminders via mail and telephone (Faulkner 2000; Guthrie 2001; Schectman 1994);
- (4) Complex behavioural approach: group sessions (Marquez 1998).

Medication—The lipid lowering medication used to treat hyperlipidaemia in the majority of trials were Statins/HMG-CoA reductase inhibitors (5 trials), followed by anion-exchange resins/bile acid sequestrants (3 trials) and niacin/nicotinic acid (2 trials). Two trials used combined medication regimen. Drug therapy was most commonly started after study allocation; only two studies included patients who were already taking lipid lowering medication (Poston 1998; Powell 1995).

Cardiovascular risk—Three trials included in this review enrolled only participants with pre-existing cardiovascular pathology or increased cardiovascular risk (Brown 1997; Faulkner 2000; Guthrie 2001), two included healthy patients with high cholesterol levels (Marquez 1998; Sweeney 1991) and another three included patients on medication for both primary and secondary prevention (Poston 1998; Powell 1995; Schectman 1994).

Settings—Two of the included trials took place in primary care (Guthrie 2001; Marquez 1998), two in secondary care (Brown 1997; Faulkner 2000) and one in both (Sweeney 1991). Other settings were local pharmacies (Poston 1998), Health Maintenance Organisations (Powell 1995) and Veteran Affairs Medical Centres (Schectman 1994). The geographical setting of most studies was the USA. One study took place in Canada and one in Spain.

Follow-up—Follow-up time was generally short, ranging from 2 to 24 months. Most studies achieved their endpoint outcomes at 3-9 months (see characteristics of included studies).

Outcome measures—The methods used to measure adherence were self-report, prescription refill rate and pill count. Self-report was used in one study asking patients if they had taken their medication as prescribed and how many doses were missed in the past 7 days (Guthrie 2001). Prescription refill rates were used by 4 studies, where refill information was obtained from pharmacies (Faulkner 2000; Poston 1998; Powell 1995; Schectman 1994). Pill counting was performed in 4 trials (Brown 1997; Faulkner 2000; Marquez 1998; Sweeney 1991). Counting pills is vulnerable to patient manipulation, and one author attempted to increase reliability of this method by performing unexpected visits to patients' homes for surprise pill counts (Marquez 1998). In another study pills were not counted in patients' view in order to avoid influencing patients' subsequent adherent behaviour (Faulkner 2000). Some authors used more than one of the above methods to measure adherence at different stages in their trials, which made comparison between trials even more difficult.

Several studies applied thresholds to define compliant behaviour i.e. proportion of patients taking more than 80% of the prescribed medication. This was considered a less valid description of compliant behaviour compared to reporting percentages of mean compliance and was therefore not reported in the tables. Discontinuation rates, frequently used as a proxy measure for adherence, were only reported in one study (Schectman 1994).

Serum lipids consisting of total cholesterol (TC), HDL, LDL and triglycerides (TRG) are physiological indicators of patient compliance and were only reported in 4 out of 8 trials (Brown 1997; Faulkner 2000; Marquez 1998; Sweeney 1991). Some trials began with a "start-up" phase where patients were either taking medication (Brown 1997) or following a diet (Sweeney 1991) before baseline blood samples were taken. Other trials took baseline blood samples immediately after recruitment.

Other reported outcome measures included side-effects experienced and reasons for non-compliance (Brown 1997; Faulkner 2000; Guthrie 2001; Marquez 1998; Schectman 1994;

Sweeney 1991). None of the studies provided data on morbidity or mortality as additional outcome measures.

Risk of bias in included studies

The four main sources of systematic bias, selection bias, performance bias, attrition bias and detection bias were all considered in the process of study assessment, as recommended by the Cochrane Reviewers' Handbook (Alderson 2004). An overall assessment of the studies was performed by categorising them into low risk of bias (if all of the above criteria were met), moderate risk of bias (one or more criteria only partly met) and high risk of bias (one or more criteria not met). Few of the reported studies provided sufficient details to replicate the methodology used to avoid bias. None of the trials met all the criteria. Only two trials were categorised as having a moderate risk of bias (Faulkner 2000; Marquez 1998). The remaining studies were deemed to have moderate to high risk of bias, given that they did not meet one or more criteria.

Blinding patients to the intervention they were receiving was not possible in this particular setting. This inevitably raises the risk of bias. Blinding of the health carer/doctor, in order to avoid systematic differences in the care provided (performance bias), is in principle possible. It was attempted in two trials, where General Practitioners were blinded to patients' group allocation in order to assure the same provision of care to both intervention and control group (Faulkner 2000; Marquez 1998). Although this is the approach of choice it has its limitations as it is vulnerable to disclosure by patients.

More than half of the studies failed to provide standard deviations (SD) or standard errors (SE), which made recalculation of the results impossible.

Effects of interventions

Types of interventions—The trials of this review aimed at increasing adherence by applying interventions as followed:

Simplification of drug regimen: Simplifying drug regimen was attempted in two studies. Reducing medication intake from four times to twice daily improved mean medication intake by 11% (96% in the intervention group (IVG) versus 85% in the control group (CG), p-value equals 0.01 (Brown 1997)). Drug modification by administering Colestyramine bars instead of powder to make intake easier decreased the adherence rate non significantly (91.8% in IVG versus 94.8% in CG, p greater than 0.05 (Sweeney 1991)). Patient preference and side effect profile was improved with twice daily intake (see the Characteristics of Included Studies Table).

Patient information and education: Pharmacist mediated information and postal back-ups successfully improved adherence in one trial (Poston 1998): videotapes, booklets and newspapers handed out by the local pharmacist followed by educational newsletters sent via post increased the adherence by 13% (92% in IVG versus 79% in CG, p equals 0.005). This applied only to the subgroup of patients newly prescribed statin treatment, but not to patients

on long term statin therapy (92% versus 91%, *p* reported as non-significant, but this was not based on a correct interaction test).

Another study attempted to increase information and education by sending out videotapes to members of a Health Maintenance Organisation, who were known to have a pharmacy claim for statins (Powell 1995). This less personal approach increased adherence rates only slightly (73% in IVG versus 70% in CG, *p* greater than 0.05).

Intensified patient care - reminding: Reinforcement and reminding via telephone and postal back-ups were the interventions of interest in three studies. Weekly phone calls were reported as improving adherence in the IVG and adherence to statins judged by prescription refill was improved by 24% (63% in IVG versus 39% in CG, *p*-value reported as less than 0.05)(Faulkner 2000).

Telephone and postal reminders in the remaining studies did not result in any significant improvement (79.7% in IVG versus 77.4% in CG, *p*-value reported as non significant) (Guthrie 2001) and 88% in IVG versus 82% in CG, *p* equals 0.32 (Schechtman 1994)).

Complex behavioural approach - group sessions: Only one trial used a group behavioural approach, where participants attended small group training (Marquez 1998). This resulted in a moderately improved adherence in the intervention group of 4.7%, which was not significant (88.5% in IVG versus 83.8% in CG, *p* greater than 0.05).

Pooling of the results—Heterogeneity is present in many areas such as background morbidity, hyperlipidaemic treatment, assessment of adherence, duration of follow-up and is indicated by the wide range of adherence levels in the control groups of the studies from 23% to 94%. Combining the data therefore did not seem appropriate.

Different classes of lipid lowering medication—No particular class of medication seemed to obtain generally higher adherence than others when simply comparing the adherence rates in the control arms of the trials. Adherence rates to medication with statins varied from 39% to 90%, with resins/bile acid sequestrants from 23% to 95% and with niacin from 84% to 85% (see characteristics of included studies).

Adherence and cholesterol—Serum cholesterol can be considered as an important marker of adherence to lipid lowering medication, but was only reported in four studies included in this review. In one RCT, a significant increase in adherence resulted in decreased serum cholesterol levels (Brown 1997). Other trials showed non significant changes of both adherence and serum cholesterol (Marquez 1998; Sweeney 1991). Faulkner et al reported an inverse relationship involving an increase in adherence with a decrease in serum levels, but the results were not confirmed by recalculation (see under characteristics of included studies in the table section).

Adherence and discontinuation rates—Discontinuation rates in addition to adherence rates were only reported in one study (Schechtman 1994). The differences between IVG and

CG were non significant for each parameter, therefore further statements about the relationship between the two measures cannot be made.

Additional studies—We found two other studies of relevance. One looked at the effect of information leaflets (Bruckert 1999), but data were never published as no effect on patient compliance had been found. Another study looking at complex interventions (pharmacist compliance feedback plus electronic and educational reminders) is pending final data analysis by Eric de Klerk and was not included in this review (see under characteristics of ongoing studies).

Summary—Three studies reported a significantly improved adherence in the intervention groups compared to the control groups. These studies were evenly spread across the groups, suggesting no advantage of one particular type of intervention. None of these studies provided standard deviations or standard errors and attempts to retrieve data from the authors were not successful (see characteristics of included studies). Subgroup analysis, cluster randomised and crossover designs were used without applying relevant statistical analysis (Brown 1997; Poston 1998) and hence results have to be considered with caution.

A combined effect on both adherence and serum lipids was only found in one study, where simplified drug regimen significantly decreased the mean total serum-cholesterol by 14 mg/dl, mean LDL by 13 mg/dl and LDL/HDL ratio by 0.17 (Brown 1997). Group behavioural approach reported a considerable and significant decrease in triglycerides of 30 mg/dl (Marquez 1998). Bar versus powder colestyramine comparison showed a non-significant difference between groups (Sweeney 1991). Faulkner et al reported a significant decrease in total serum cholesterol, LDL and triglycerides, but recalculation did not confirm these results. Outcomes obtained at the endpoint of each trial are shown in more detail in the Characteristics of Included Studies Table.

DISCUSSION

Findings

The majority of studies did not increase adherence significantly by informing, reminding and motivating patients. Particular types of interventions did not seem to be more effective than others. It is emphasised that adherence rates were very variable, which makes comparison between trials difficult.

Limitations of this review

Measuring adherence—A variety of measures for adherence have been used. In this review, we only included trials reporting levels of adherence in terms of adherence rates. Studies using proxy measures for adherence such as discontinuation rates, adverse effects or physiological indicators do exist, but the relationship between those measures and levels of adherence remains unclear.

Comparing adherence levels between trials—Heterogeneity between trials makes direct comparison and pooling of the data inappropriate. Even important factors, such as the class of medication used, did not influence adherence rates as one would have expected. In

this review, treatment with statins were not associated with higher adherence levels. This was surprising, considering that adherence to statins in general is thought to be higher than to niacin or resins due to fewer side effects (Avorn 1998; Eriksson 1998; Tsuyuki 2001). It indicates that the class of medication is only one of many factors affecting adherence and highlights the difficulty of comparing adherence rates between trials.

Underestimating the treatment effect—The difficulties in measuring adherent behaviour accurately and reliably is one of the main limitations of this review. An agreement on the ‘gold standard’ does not exist and the current reality in adherence research is the co-existence of different methods. Refill-records, patient self-report and pill count have been shown to overestimate adherence when compared to newer methods such as electronic monitoring of pill use or chemical markers (Maenpaa 1987; Roter 1998; Straka 1997; Urquhart 1994). The older methods used in the trials of this review may in part explain the high adherence levels in both intervention and control groups. If starting levels of adherence are high, it may reduce the effect sizes and lead to an underestimation of the intervention effect. This is known as a ‘ceiling effect’ (Dolan 1985).

Activities to follow up adherence might have a similar effect: phone calls or interviews to assess patient behaviour might act as an unintended intervention and increase adherence rates generally.

Methodological and analytical weaknesses—The quality of the studies in this review was generally low. Investigators assessing adherence in trials were often not blinded towards the interventions patients received and risk of bias was high in the majority of studies. The presentation of statistical analyses often omitted crucial details, so that the results could not be verified. When sufficient information was given, results were at times not consistent with our own calculations.

The analysis of covariance method when comparing serum lipid levels between groups was only applied by one study (Sweeney 1991). It takes into account the different baseline values in intervention and control group leading to more reliable results than is obtained by just comparing the mean endpoint values of each group. The baseline value was taken into consideration by another trial, comparing the proportional change from baseline in both groups (Faulkner 2000). The remaining trials compared endpoints only and did not adjust for baseline differences between intervention and control group at follow-up.

Study design—Results of crossover designs analysed in the same way as parallel group trials have to be considered with caution, as results of intervention and control groups are treated as if they came from an independent group of patients, which is clearly not the case (Clarke 2002). Poorly analysed cluster randomised trials are likely to over-estimate the statistical significance of the treatment effect, as observations in one cluster tend to be more similar to each other than to individuals of the rest of the sample. As a result standard errors and p-values may be too small and confidence intervals may be too narrow. Similarly, subgroup analysis should not be performed by just analysing the intervention effect in both subgroups, but should apply appropriate statistical tests for interaction (Assmann 2000).

Significance and size of the intervention effect are therefore questionable in the crossover (Brown 1997) and cluster randomised trials (Poston 1998) included in this review.

AUTHORS' CONCLUSIONS

Implications for practice

Despite efforts to increase the use of lipid lowering medication and despite the fact that poor adherence to medication is common, randomised controlled trials in this area are very limited in both number and quality. At this stage, no adherence-enhancing intervention can be recommended in clinical practice.

Implications for research

The majority of interventions described in this review only focus on one or two aspects of adherence. The phenomenon of adherence is complex and it would seem reasonable for interventions to address this complexity with a more patient-centred approach (Schroeder 2004a). It has been stated that patients' beliefs and preferences need to be acknowledged more, being one of the most prevalent influences on medicine taking (RPS 1997). A combination of strategies including information, reminding, adherence reinforcement and emphasis on the patient's perspective might lead to more conclusive answers in further research.

The lack of a valid method for measuring adherence remains another obstacle to high quality research. Electronic monitoring could help to provide more detailed and reliable results in the pattern of adherence.

Other important aspects for further RCTs are long-term follow up, combination of adherence and serum lipid records, rigorous methodology, sufficient power and, eventually, the inclusion of economic analyses.

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External sources

- No sources of support supplied

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Brown 1997

Methods	Pill count Follow up at 8 months
Participants	n = 29 high CHD risk 100% male Mean age 49 Participants subgroup of FAT study
Interventions	Niacin 1000mg twice daily (IVG (intervention group)) versus Niacin 500 mg four times daily (CG (control group)) Both groups were on triple therapy consisting of niacin , lovastatin (20mg twice daily) and colestipol (10gr twice daily)
Outcomes	<ol style="list-style-type: none"> ADHERENCE mean adherence : 96% (IVG) versus 85% (CG) difference in mean adherence between groups: 11% p = 0.01 SERUM LIPIDS Endpoints compared Significant difference in total cholesterol : 158 mg/dl (IVG) versus 172 mg/dl (CG) p< 0.05 Significant difference in LDL 85 mg/dl (IVG) versus 98 mg/dl (CG) p<0.005 Significant difference in LDL/HDL ratio 1.66 (IVG) versus 1.83 (CG) p<0.02 (provided retrospectively by author as accidentally omitted in paper). Recalculation not performed due to missing standard deviations. ADVERSE EFFECTS Less flushing reported in IVG 14/29 patients without flushing (IVG) versus 6/29 (CG) p reported as < 0.005 patient preference higher in IVG (21/29 versus 4/29, p less than 0.02)
Notes	crossover design, results have to be considered with caution (see 'limitation of this review') subgroup of bigger trial high to moderate risk of bias Some issues about the data (omission of p-value) were clarified and confirmed in helpful correspondence with the author

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Faulkner 2000

Methods	<ol style="list-style-type: none"> ADHERENCE <ol style="list-style-type: none"> Short term pill count at week 12 long term prescription refill rate at two years SERUM LIPIDS <ol style="list-style-type: none"> Short term Total Cholesterol (TC), LDL,HDL and Triglycerides at 12 weeks Long term Total Cholesterol, LDL,HDL and Triglycerides at 2 years
Participants	n=30 (15 in each group) patients seen in secondary care post cardiac surgery 53% male patients in IVG / 60% male patients in CG Mean age 64 years in IVG / 61 years in CG USA

Interventions Weekly phone calls by same pharmacist for 12 weeks for information, education and drug counselling.
Emphasis on prevention.
Both IVG and CG were started on statins and resins post allocation, as well as given drug instructions and dietary advice.
Medication used : Lovastatin 20 mg once daily and colestipol (anion-exchange resin) 5 mg twice daily

Outcomes	1	ADHERENCE
	1.1	short term outcomes reported were non significantly improved for both Statin and Colestipol mean adherence was 88% in IVG versus 86% in CG (Statin) mean adherence was 90% in IVG versus 88% in CG (Colestipol) p-value reported as > 0.05 for both
	1.2	Long term outcomes reported were significantly improved for both Statin and Colestipol mean adherence was 63% in IVG versus 39% in CG (Statin) mean adherence was 48% in IVG versus 23% in CG (Colestipol) P-value reported as <0.05 for for both Recalculating results was not possible as standard deviations were not reported.
	2	SERUM LIPIDS
	2.1	Short term outcomes were reported as non significant differences for cholesterol, LDL, HDL and triglycerides in IVG and CG. The percent change from baseline was compared between IVG and CG. 5.4% greater reduction for TC 5.2% greater reduction for LDL 0.1% greater reduction for HDL 2.6% greater reduction for TRG p-value was reported as > 0.05 hence non significant for all Recalculated p-values (ttest/Stata) confirmed these results.
	2.2	Long term outcomes were reported as significant changes for TC, LDL and TRG. These results could not be confirmed by recalculation. Proportional reduction from baseline compared between IVG and CG: 9.1% greater reduction in IVG for TC (p reported < 0.03, if recalculated p = 0.38) 9.9% greater reduction in IVG for LDL (p reported < 0.02, if recalculated p = 0.25) 0.8% greater reduction in IVG for HDL (p reported < 0.45, if recalculated p = 0.78) 6.3% greater reduction in IVG for TRG (p reported < 0.04, if recalculated p = 0.30) Telephone education and reminders improved lipid profile significantly at long term follow up. Very similarly long term but not short term adherence showed a significant improvement in the intervention group compared to the control group. Recalculation did not confirm results for serum lipids. Adherence result could not be confirmed by recalculation as no standard deviations were reported and data was irretrievable Minor error in table III (wrong baseline TC) was detected, which would have had no major impact as only underestimating intervention effect

Notes Moderate risk to bias. Good study design, long follow-up (2 years).
The fact that the p-values for the lipid results could not be reproduced by our own calculations, casts some doubt upon the outcome for adherence

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Guthrie 2001

Methods	Self reported adherence via questionnaire at 6 months expressed as percentage of patients taking medication as prescribed
Participants	n = 4548 (3635 in IVG / 913 in CG) 13100 initially recruited (10335 in IVG / 2765 in CG), response rate only 35% (35% in IVG / 33% in CG) Patients with high risk of MI Primary care setting mostly (90%) 49% male patients in IVG / 47% in CG Mean age 57 years in IVG/ 58 years in CG USA
Interventions	Telephone reminders and early postal reminders in IVG.

Both IVG and CG were started on pravastatin (dose not reported), received lifestyle modification advice by their physician and were sent late postal reminders		
Outcomes	According to the authors, there were no significant difference in adherence between IVG and CG. 79.7% of patients in the IVG took their medication as prescribed compared to 77.4% of patients in the CG. Reporting of side effects in patients who had terminated their medication were similar in IVG and CG (5.5% versus 5.3%) P-values, standard deviations and power calculations were NOT reported	
Notes	The outcome might have been contaminated by sending late postal reminders to patients belonging to the control group. Self report data remained unclear and could not be retrieved from the author of the study. Overall high risk to bias.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Marquez 1998

Methods	Pill counts over 4 months. Surprise pill counts to patients' homes were performed to reduce potential patient manipulation	
Participants	n = 110 (55 in each group) Patients started on lipid lowering medication for mostly primary prevention Primary care setting in Spain. 35% male in IVG / 41% male in CG Mean age 55.7 years in IVG / 56.1 in CG	
Interventions	Small group training followed by postal back-up consisting of information packages (IVG only). Both IVG and CG were started on fluvastatin 20 mg once daily post allocation and received verbal and written information followed by usual care by their General Practitioner	
Outcomes	1	ADHERENCE No significant difference between IVG and CG (mean percentage of pills taken). 88.5% of prescribed pills were taken by patients in IVG versus 83.8% in CG. Difference = 4.7%. p reported as > 0.05 This result was confirmed by recalculated p = 0.084 (ttesti, STATA)
	2	SERUM LIPIDS Differences between IVG and CG only significant for TRG. Compared were the final mean endpoint values between groups. 7.5 mg/dl more reduction in mean TC in IVG , p > 0.05 p=0.26 * 5.2 mg/dl more reduction in mean LDL in IVG, p> 0.05 p=0.48 *
	2.1	mg/dl increase in mean HDL in IVG p> 0.05 p=0.48 * 30 mg/dl more reduction in mean TRG in IVG p < 0.05 p=0.0019* *p-value if recalculated (ttesti, Stata)
	3.	ADVERSE EFFECTS Reported adverse effects lower in IVG (5.5% versus 9.2%, p reported as non significant)
Notes	Complex intervention. Surprise pill count might increase reliability of adherence results. Short follow up. Only final endpoints compared, they were not adjusted for baseline. Low risk to bias.	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Poston 1998

Methods	Adherence judged by prescription refill rates during 9 months	
Participants	BN= 455 (231 in IVG/224 in CG) Cluster randomised trial involving 54 pharmacies (26 IVG/28 CG) Areas "similar in population" in Canada Primary and secondary prevention New or long term prescribing of statins Age and gender unknown	
Interventions	1	Pharmacist mediated counselling and information (videotape,booklet,newsletter)
	2	Newsletter back-up via post Both IVG and CG were under therapy with Simvastatin and Lovastatin at different dosages. Both groups received follow-up telephone calls at 2,5 and 8 months (medication-taking behaviour, demographic information)
Outcomes	Results were only presented in subgroup analysis: 1 Adherence in subgroup of patients on newly prescribed Statins was significantly improved by th intervention 91.9% in IVG versus 79.2% in CGp <= 0.005 2 Adherence in subgroup of patients on repeat prescription of Statins was slightly and NOT significantly improved 92.2% in IVG versus 90.6% in CG p reported as non significant Standard deviations were not reported.	
Notes	Only presented as subgroup analysis. The cluster randomised design might lead to an overestimation of the effects,as clustering is not allowed for in the analysis. Losses in IVG and CG not clearly stated.	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Powell 1995

Methods	Adherence assessed via prescription refill records for a period of 3 to 9 months	
Participants	N=568 (271 in IVG/ 297 in CG) Members of a Health Maintenance Organisation (HMO) on current medication with Simvastatin. Primary and secondary prevention Age and gender not reported USA	
Interventions	Videotape was sent to members allocated to IVG. Content: explanation of disease, drug action and side effects, reinforcing importance of compliance. Duration: 30 minutes Recipients were blinded to adherence outcome of study. CG did not receive any contact.	
Outcomes	Adherence improved moderately in the IVG, the changes were NOT significant 73% (SD 28) in IVG versus 70% in CG (SD 26) p > 0.05 if recalculated p = 0.19	
Notes	The result only to this particular impersonal way of delivering information and behavioural advice, hence the effect of the videotape intervention might be underestimated. It remains unknown how many people actually had the appropriate equipment to access it. Delivering the videotape in a personal setting could have increased the interventional effect	

Risk of bias

Item	Authors' judgement	Description
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Allocation concealment? Unclear

B - Unclear

Schechtman 1994

Methods	Medication adherence assessed	
	1	Via prescription refill rates for 2 months
	2	Via self-reported discontinuation rates
	3	Via interview
Participants	n= 40 (18 in IVG / 22 in CG) in patients taking bile acid sequestrants (cholestyramine 8g twice daily) n= 80 (40 in IVG / 40 in CG) in patients taking Nicotinic acid (niacin 0.5 g three times daily) Newly prescribed lipid lowering medication for primary and secondary prevention Mean age 59 years in IVG/ 62 years in CG mostly male participants	
Interventions	Telephone contacts to encourage drug continuation (5 contacts in the first month). Both IVG and CG received oral and written information prior to drug prescription	
Outcomes	1	Moderate, non significant adherence improvement by early telephone calls in both medication groups in the first 2 months (script refills). BAS group: 88% (SE 4) in IVG versus 82% (SE 4) in CG p=0.32 NIACIN group: 90%(SE 2) in IVG versus 84% (SE 3) in CG p=0.07
	2	Moderate, non significant increase (BAS) or decrease(NIACIN) in discontinuation rates in both medication groups after 6 months (self report). BAS group: 48% in IVG versus 39% in CG p=0.17 NIACIN group: 29% versus 34% p=0.87 Standard errors of discontinuation rates were NOT reported.
	3	Adherence assessed via interview was generally lower, but showed a similar pattern of moderate nonsignificant improvement i the intervention groups
Notes	Adherence rates in this study do not reflect a mean percentage value like in other studies. Only patients remaining on treatment are included, excluding patients who discontinued their medication. Numbers in BAS group are too low to detect a difference in adherence of 15% according to power calculations performed by the authors. Numbers, non-responders and drop-outs remain unclear.	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Sweeney 1991

Methods	Adherence assessed via pill count over 2 months
Participants	n=83 (45 in IVG / 38 in CG) ambulatory care Primary prevention 49% male in IVG / 44% male in CG mean age: 55.3 years in IVG/ 55.5 in CG
Interventions	Anion-exchange resins in two different forms: colestyramine (8g twice daily) in bar form (IVG) versus colestyramine (8g twice daily) in powder form (CG).
Outcomes	Mean adherence rate for bar form slightly worse compared with powder form. Difference non significant.

91.8% (SE3.6) in IVG versus 94.8 (SE 2.1) in CG
 $p > 0.05$
 if recalculated $p = 0.47$

Notes	Bar form versus powder is very specific for colestyramine and not relevant for other lipid lowering medication. Follow up is short.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Allen 2000	Adherence outcome only in a subgroup of patients
Allen 2002	Review
Alvarez 2001	Review
Anon 2001(a)	No random allocation.
Anon 2001(b)	Congress report
Anon 2002	No adherence outcome reported
Ashcroft 2001	Report
Athyros 2002b	Intervention not aimed at improving medication adherence
Baillargeon 2001	No RCT design
Becker 1998	Intervention aimed at improved prescribing
Becker 2001	Review
Bogden 1997	intervention not aimed at improving medication adherence
Bozovich 2000	Non-random allocation
Bruckert 1999	Subtrial looking at information leaflets as adherence-enhancing intervention. Data are not available and were never published due to non significant effect
Burkett 1990	Intervention not aimed at improving medication adherence
Casebeer 1999	Intervention aimed at influence physicians' behaviour
Coates 1982	Intervention not aimed at improving adherence to hypolipidaemics
Copher 2002	Before/after comparison
DeBusk 1994	No adherence outcome reported.
Diabetes 2000	Intervention not aimed at improving medication adherence
Ditusa 2001	No RCT
Diwan 1995	Intervention aimed at influence physicians' behaviour
Dobs 1994	Intervention not aimed at improving medication adherence
Dunham 2000	No adherence outcome
Ebrahim 2000	Review
Ellis 1998	Comment
Ellis 2000	Intervention not aimed at patient adherence
Eriksson M, Had2	Adherence comparison of classes of hypolipidemics

Frances 2001	Intervention not aimed at patient adherence
Friedman 1998	Intervention not aimed at medication adherence
Gaede 1999	Intervention not aimed at improving medication adherence
Gaede 2003	Intervention not aimed at improving medication adherence
Insull 1997	Review
Ives 1993	Intervention not aimed at improving medication adherence
Jackevicius 2002	Cohort study
Johannesson 1996	No adherence outcome reported
Jolly 1998	Not concerned with lipidaemia
Keyserling 1997	Intervention not aimed at improving medication adherence
Kim 2002	Observational study
Kinn 2001	No RCT
Kiortsis 2000	Cross sectional study
Kirkman 1994	Intervention not aimed at improving medication adherence
Kjelsberg 1990	Intervention not aimed at improving medication adherence
Konzem 1997	No random allocation
Kuznar 2002	Comment
LaRosa 2000	Review
LaRosa JH, LaRo2	Review
Lesaffre 2000 1	Not concerned with lipidaemia
Lindholm 1996	Intervention not aimed at improving medication adherence
Merriam 1997	Intervention not aimed at improving medication adherence
Micevski 2002	Review
Moher 2001	Intervention aimed at influence prescribing
Noel 2002	Letter
O'Donnell 2001-1	No RCT design
O'Donnell 2001-2	No RCT design
Oi 1998	No adherence outcome reported
Pineiro 1997	No RCT design
Rachmani 2002	No adherence outcome reported
Rastam 1996	Intervention not aimed at improving medication adherence
Rindone 1998	No adherence outcome reported
Robin 2002	Review
Rodgers 2000	Review
Schectman 1996	Only maintainance rates in subgroup reported
Scherwitz 1995	Intervention not aimed at improving medication adherence
Schwed 1999	No RCT design
Senaratne 2001	No RCT design
Shaffer 1995	Intervention not aimed at improving medication adherence
Shively 1991	Review

Simpson 2001	Intervention not aimed at improving medication adherence
Tsuyuki 1999	Intervention not aimed at improving medication adherence
Tsuyuki 2002	Review
Tully 2000	Review
Urquhart 1999	Review
Vale 2002	Adherence outcome not reported
Velonakis 1999	No random allocation
Verges 1998	No random allocation
Wahlstrom 1995	Intervention aimed at influence prescribing
Wei 2002	No RCT design
Wright 2002	Reveiw
Zermansky 2002	Not concerned with lipidaemia

Characteristics of ongoing studies [ordered by study ID]

De Klerk 2003

Trial name or title	Improved compliance and persistence with atorvastatin through a pharmacy -based intervention
Methods	
Participants	393 patients with elevated cholesterol levels and on Atorvastatin IVG n= 194 CG n= 199
Interventions	pharmacist review, electronic and educational reminding
Outcomes	Intervention improved patient adherence and persistence with atorvastatin. prescribed dosis taken 98.9% (IVG) versus 95.2% (CG), p< 0.001
Starting date	not reported
Contact information	Eric de Klerk
Notes	abstract submitted to ISPOR

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1
Search Strategy for CENTRAL

Issue 1, 2003	
#1	compliance
#2	non-compliance
#3	noncompliance
#4	adher*

Issue 1, 2003

#5	PATIENT COMPLIANCE
#6	TREATMENT REFUSAL
#7	PATIENT DROPOUTS
#8	nonadherence*
#9	non-adherence*
#10	nonadherence
#11	(refusal or refuse*)
#12	(improv* near (follow next up*))
#13	(improv* near follow-up*)
#14	dropout*
#15	(drop next out*)
#16	(abandon* near treatment*)
#17	(stop* near treatment*)
#18	(patient near attitude*)
#19	(patient near acceptance)
#20	ATTITUDE TO HEALTH
#21	PATIENT SATISFACTION
#22	(patient next satisfaction)
#23	COUNSELING
#24	PATIENT CARE
#25	HEALTH BEHAVIOR
#26	PATIENT EDUCATION
#27	BEHAVIOR THERAPY
#28	NURSE PRACTITIONERS
#29	PHARMACISTS
#30	counsel*
#31	nurse*
#32	pharmacist*
#33	(patient next education*)
#34	(pharmacy or pharmacies)
#35	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11)
#36	(#12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22)
#37	(#23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34)
#38	(#35 or #36 or #37)
#39	HYPERLIPIDEMIA
#40	ANTILIPEMIC AGENTS
#41	hypercholesterol*
#42	hypercholesterol*
#43	hyperlipid*
#44	statin*
#45	antilipid*
#46	hyperlip*

Issue 1, 2003

- #47 dyslip*
- #48 (lipid next lowering)
- #49 (cholesterol next lowering)
- #50 antilipemic
- #51 hypocholesterolemic
- #52 (hydroxymethylglutaryl near inhibitor*)
- #53 atorvastatin
- #54 cerivastatin
- #55 pravastatin
- #55 simvastatin (#39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48)
- (#49 or #50 or #51 or #52 or #53 or #54 or #55 or #55)
- (#56 or #57)
- (#38 and #58)

Table 2
Search Strategy for EMBASE

Jan1998 to Feb 2003

- 1 exp hyperlipidemia/
- 2 exp antilipemic agents/
- 3 hypercholesterol\$.tw.
- 4 hyperlipid\$.tw.
- 5 statin\$.tw.
- 6 antilipid\$.tw.
- 7 hyperlip?emia.tw.
- 8 dyslip?emia.tw.
- 9 lipid lowering.tw.
- 10 or/1-9
- 11 exp Counseling/
- 12 patient care/
- 13 Health Behavior/
- 14 exp Patient Education/
- 15 exp Behavior Therapy/
- 16 behavior modification/
- 17 (behavi\$ adj3 (modif\$ or therap\$ or adjust\$)).tw.
- 18 Nurse Practitioners/
- 19 Pharmacists/
- 20 (nurse adj3 (led\$ or manage\$ or program\$)).tw.
- 21 counsel\$.tw.
- 22 nurse based.tw.
- 23 (nurse adj3 based).tw.

Jan1998 to Feb 2003

- 24 patient education\$.tw.
- 25 (patient\$ adj3 educat\$).tw.
- 26 ((nurse\$ or pharmac\$) adj3 (led\$ or manage\$ or program\$ or based\$)).tw.
- 27 or/11-26
- 28 (adher\$ or nonadherence\$ or non-adherence\$).tw.
- 29 (compliance\$ or noncompliance\$ or non-compliance\$).tw.
- 30 (refusal or refuse\$).tw.
- 31 (improv\$ adj5 (follow-up or follow up)).tw.
- 32 (dropout\$ or drop-out\$ or drop-out\$).tw.
- 33 (patient\$ adj3 (attitude\$ or acceptance\$ or satisfaction\$)).tw.
- 34 (treatment\$ adj3 (stop\$ or abandon\$)).tw.
- 35 patient compliance/
- 36 Patient Attitude/
- 37 Illness Behavior/
- 38 patient satisfaction/
- 39 or/28-38
- 40 10 and 39

Table 3
Search Strategy for CINAHL

Jan 1982 Feb 2003

- 1 exp Patient Compliance/
- 2 exp Treatment Refusal/
- 3 exp Patient Dropouts/
- 4 exp Attitude to Health/
- 5 exp Patient Satisfaction/
- 6 (adher\$ or nonadherence\$ or non-adherence\$).tw.
- 7 (compliance\$ or noncompliance\$ or non-compliance\$).tw.
- 8 (refusal or refuse\$).tw.
- 9 (improv\$ adj 5 (follow-up or follow up)).tw.
- 10 (dropout\$ or drop-out\$ or drop-out\$).tw.
- 11 (patient\$ adj3 (attitude\$ or acceptance\$ or satisfaction\$)).tw.
- 12 (treatment\$ adj3 (stop\$ or abandon\$)).tw.
- 13 or/1-12
- 14 exp hyperlipidemia/
- 15 exp antilipemic agents/
- 16 hypercholesterol\$.tw.
- 17 hyperlipid\$.tw.
- 18 statin\$.tw.
- 19 antilipid\$.tw.

Jan 1982 Feb 2003

- 20 hyperlip?emia.tw.
 - 21 dyslip?emia.tw.
 - 22 lipid lowering.tw.
 - 23 or/14-22
 - 24 exp Counseling/
 - 25 patient care/
 - 26 Case Management/
 - 27 Health Behavior/
 - 28 exp Patient Education/
 - 29 exp Behavior Therapy/
 - 30 (behavi\$ adj3 (modif\$ or therap\$ or adjust\$)).tw.
 - 31 Nurse Practitioners/
 - 32 Pharmacists/
 - 33 (nurse adj3 (led\$ or manage\$ or program\$)).tw.
 - 34 counsel\$.tw.
 - 35 nurse based.tw.
 - 36 (nurse adj3 based).tw.
 - 37 patient education\$.tw.
 - 38 (patient\$ adj3 educat\$).tw.
 - 39 ((nurse\$ or pharmac\$) adj3 (led\$ or manage\$ or program\$ or based)).tw.
 - 40 or/24-39
 - 41 13 and 23
 - 42 23 and 40
 - 43 42 not 41
 - 44 Randomized controlled trials/
 - 45 clinical trial.pt.
 - 46 exp Clinical trials/
 - 47 (clin\$ adj25 trial\$).ti,ab. (5610)
 - 48 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)).ti,ab.
 - 49 placebos.sh.
 - 50 placebo\$.ti,ab.
 - 51 random\$.ti,ab.
 - 52 exp evaluation studies/
 - 53 prospective studies.sh.
 - 54 (control\$ or prospectiv\$ or volunteer\$).ti,ab.
 - 55 or/44-54
 - 56 43 and 55
-

Table 4
Search Strategy for PsychINFO

Jan 1972 Feb 2003	
#45	#44 not #34(67 records)
#44	((educat*) or (pharmacist* or pharmacy or pharmacies) or ("Health-Behavior" in DE) or (nurse*) or (counsel*) or ("Pharmacists-" in DE) or ("Cognitive-Therapy" in DE) or (explode "Counseling-" in DE)) and (((CLINICAL-TRIAL in PT:PY) or (random*) or (clinical trial*) or (controlled study) or ((double-blind) or (double blind)) or ("Placebo-" in DE) or (placebo*) or (clinical* stud*) or ((single-blind) or (single blind) or (triple-blind) or (triple blind)) or ((comparative stud*) or (control* stud*))) and ((lipid*) or (antilipid*) or (statin*) or (hypercholesterol*) or (hyperlipid*) or (hyperlipidemi*) or (antilipemic*) or (lipid lower*)) or (cholesterol))(75 records)
#43	(educat*) or (pharmacist* or pharmacy or pharmacies) or ("Health-Behavior" in DE) or (nurse*) or (counsel*) or ("Pharmacists" in DE) or ("Cognitive-Therapy" in DE) or (explode "Counseling-" in DE) (363511 records)
#42	educat*(290103 records)
#41	"Health-Behavior" in DE(5756 records)
#40	counsel*(73170 records)
#39	pharmacist* or pharmacy or pharmacies(3150 records)
#38	nurse*(19261 records)
#37	"Pharmacists-" in DE(153 records)
#36	"Cognitive-Therapy" in DE(7875 records)
#35	explode "Counseling-" in DE(28948 records) Searches and results below from saved search history adherence_stats 18 12 02
#34	((lipid*) or (antilipid*) or (statin*) or (hypercholesterol*) or (hyperlipid*) or (hyperlipidemi*) or (antilipemic*) or (lipid lower*)) or (cholesterol) and ((adhere* or nonadhere* or non-adhere*) or ("Treatment-Compliance" in DE) or ("Treatment-Refusal" in DE) or ("Treatment-Dropouts" in DE) or (compliance* or noncompliance* or non-compliance*) or ("Client-Attitudes" in DE))) and (((CLINICAL-TRIAL in PT:PY) or (random*) or (clinical trial*) or (controlled study) or ((double-blind) or (double blind)) or ("Placebo-" in DE) or (placebo*) or (clinical* stud*) or ((single-blind) or (single blind) or (triple-blind) or (triple blind)) or ((comparative stud*) or (control* stud*))) and ((adhere* or nonadhere* or non-adhere*) or ("Treatment-Compliance" in DE) or ("Treatment-Refusal" in DE) or ("Treatment-Dropouts" in DE) or (compliance* or noncompliance* or non-compliance*) or ("Client-Attitudes" in DE)))(13 records)
#33	((CLINICAL-TRIAL in PT:PY) or (random*) or (clinical trial*) or (controlled study) or ((double-blind) or (double blind)) or ("Placebo-" in DE) or (placebo*) or (clinical* stud*) or ((single-blind) or (single blind) or (triple-blind) or (triple blind)) or (comparative stud*) or (control* stud*)) and ((adhere* or nonadhere* or non-adhere*) or ("Treatment-Compliance" in DE) or ("Treatment-Refusal" in DE) or ("Treatment-Dropouts" in DE) or (compliance* or noncompliance* or non-compliance*) or ("Client-Attitudes" in DE))(1674 records)
#32	((lipid*) or (antilipid*) or (statin*) or (hypercholesterol*) or (hyperlipid*) or (hyperlipidemi*) or (antilipemic*) or (lipid lower*)) or (cholesterol) and ((adhere* or nonadhere* or non-adhere*) or ("Treatment-Compliance" in DE) or ("Treatment-Refusal" in DE) or ("Treatment-Dropouts" in DE) or (compliance* or noncompliance* or non-compliance*) or ("Client-Attitudes" in DE))(101 records)
#31	(lipid*) or (antilipid*) or (statin*) or (hypercholesterol*) or (hyperlipid*) or (hyperlipidemi*) or (antilipemic*) or (lipid lower*)) or (cholesterol)(3874 records)
#30	lipid*(1612 records)
#29	cholesterol(1438 records)
#28	(antilipid*) or (statin*) or (hypercholesterol*) or (hyperlipid*) or (hyperlipidemi*) or (antilipemic*) or (lipid lower*)(1288 records)
#27	antilipid*(2 records)
#26	statin*(1082 records)
#25	hypercholesterol*(104 records)
#24	hyperlipid*(82 records)
#23	hyperlipidemi*(77 records)

Jan 1972 Feb 2003

#22	anti-lipemic*(0 records)
#21	antilipaemic*(0 records)
#20	antilipemic*(2 records)
#19	lipid lower*(31 records)
#18	(CLINICAL-TRIAL in PT:PY) or (random*) or (clinical trial*) or (controlled study) or ((double-blind)or (double blind)) or ("Placebo-" in DE) or (placebo*) or (clinical* stud*) or ((single-blind) or (single blind) or (triple-blind) or (triple blind)) or ((comparative stud*) or (control* stud*)) (75728 records)
#17	(comparative stud*) or (control* stud*) (12663 records)
#16	(single-blind) or (single blind) or (triple-blind) or (triple blind) (467 records)
#15	clinical* stud* (4476 records)
#14	placebo* (14487 records)
#13	"Placebo-" in DE (1117 records)
#12	(double-blind) or (double blind) (7946 records)
#11	controlled study (2167 records)
#10	clinical trial* (4185 records)
#9	random* (45203 records)
#8	CLINICAL-TRIAL in PT:PY (3367 records)
#7	(adhere* or nonadhere* or non-adhere*) or ("Treatment-Compliance" in DE) or ("Treatment-Refusal" in DE) or ("Treatment-Dropouts" in DE) or (compliance* or noncompliance* or non-compliance*) or ("Client-Attitudes" in DE) (22439 records)
#6	"Client-Attitudes" in DE (6128 records)
#5	compliance* or noncompliance* or non-compliance* (11645 records)
#4	"Treatment-Dropouts" in DE (1339 records)
#3	"Treatment-Refusal" in DE (272 records)
#2	"Treatment-Compliance" in DE (4478 records)
#1	adhere* or nonadhere* or non-adhere* (5154 records)

WHAT'S NEW

Last assessed as up-to-date: 31 July 2004.

Date	Event	Description
9 September 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 2003

Review first published: Issue 4, 2004

Date	Event	Description
1 August 2004	New citation required and conclusions have changed	Substantive amendment

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**Indicates the major publication for the study*

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PLAIN LANGUAGE SUMMARY

People at risk or suffering from cardiovascular disease need to be encouraged to take drugs which decrease blood lipids (lipid lowering medication/cholesterol lowering medication)

Lipid lowering medication has been shown to be very effective in the prevention of heart attack and stroke. People can find it difficult to take their medicines as prescribed, and this is thought to be an important factor in treatment failure. Doctors are keen for patients to take their medication at the right dosage and long term. This review of trials reports interventions to improve patients' drug taking behaviour (medication adherence). It shows that so far no specific type of intervention has been found to be particularly successful.