How can adherence to lipid-lowering medication be improved? A systematic review of randomized controlled trials

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\textbf{Objective.} Poor patient adherence to lipid-lowering medication is a major contributory factor in the lack of success in treating hyperlipidaemia. The objective of this review was to assess the effect of adherence-enhancing interventions for lipid-lowering medication.

\textbf{Design.} Systematic review of randomized controlled trials (RCTs). Data sources: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PsycInfo and CINAHL for all-language publications in November 2005. Direct contact with authors of included RCTs.

\textbf{Methods.} Two reviewers extracted data independently and assessed studies according to criteria outlined by the Cochrane Reviewers’ Handbook.

\textbf{Results.} Nine RCTs were included in the review. Substantial between-study heterogeneity made pooling of data inappropriate. Four out of nine RCTs reported significantly improved adherence rates. The interventions associated with improved adherence were simplification of drug regimen (absolute increase 11%), patient information and education (13%) and intensified patient care (8.6% and 24%). Duration of follow-up was short, ranging from 2 to 24 months. No clear pattern emerged with regard to different classes of lipid-lowering drugs and adherence levels.

\textbf{Conclusions.} Intensified patient care appears to be the most promising intervention in terms of improved adherence to lipid-lowering drugs. Numbers of trials are low and evidence is sparse. Important aspects to be addressed in future studies are long-term follow-up, effect of improved adherence on serum lipid levels and concurrent, economic evaluation of adherence-enhancing strategies.

\textbf{Background}

Hyperlipidaemia is an important risk factor for coronary heart disease.\textsuperscript{1} There is compelling evidence about the effectiveness of lipid-lowering drugs in reducing lipid levels and reducing the risk of heart attacks and stroke.\textsuperscript{2} Adherence is defined as the extent as to which patients take medication as prescribed and is determined by a variety of factors such as health beliefs, risk perception, poor knowledge, denial, adverse drug effects and poor memory.\textsuperscript{3} The importance of the patient’s agreement and the significance of the patient’s role within the doctor–patient relationship have been emphasized, and compliance has been replaced by more patient-centred synonyms such as adherence and concordance.\textsuperscript{4–6}

High discontinuation rates and lack of adherence to cholesterol-lowering medication have been shown to be important factors in treatment failure in terms of achieving treatment goals as well as being associated with an increase in mortality.\textsuperscript{7,8} The treatment of a symptomless condition such as hyperlipidaemia signifies a particular challenge to both doctor and patient. Epidemiological data show that target cholesterol concentrations are only achieved in fewer than 50% of people receiving cholesterol-lowering drugs.
and that only one in four patients continued taking cholesterol-lowering drugs long-term.\textsuperscript{9,10} Primary prevention trials appear to have higher discontinuation rates than secondary prevention trials indicating a relationship between adherence and awareness of illness.\textsuperscript{11,12}

The aim of this systematic review was to assess the effects of interventions designed to help people take their lipid-lowering medication in ambulatory settings.

Methods

Literature search

The search for original randomized controlled trials (RCTs) was conducted in November 2005 using a search developed by the Cochrane Heart Group. It included articles of all languages from any year in the Cochrane Central Register of Controlled Trials (CENTRAL) on The Cochrane Library, MEDLINE, EMBASE, PsycInfo and CINAHL (Fig. 1). In addition, we searched reference lists of retrieved papers and contacted study authors and experts in the field for additional information on further published and unpublished studies.

Study selection

Following the initial search, two reviewers selected studies independently by assessing titles and abstracts. Full-text articles of potential relevance were obtained. Following this initial screening, studies were selected by applying the following inclusion criteria:

- Studies were RCTs, where care in the intervention group was compared to patients who received no intervention or usual care.
- Population of interest were adults prescribed lipid-lowering medication for primary or secondary prevention of cardiovascular disease in ambulatory care settings.
- Interventions aimed to increase adherence to lipid-lowering medication, and were categorized as simplification of drug regimen, patient information and education, intensified patient care and complex behavioural approach.
- Outcomes were adherence to medication measured in the following ways: indirect measures (e.g. pill count, prescription refill rate, electronic monitoring), subjective measures (e.g. patients' self-report in diaries, interviews) and direct measures of adherence (tracer substances in blood or urine). Two additional outcomes were also recorded: physiological indicators (e.g. total cholesterol, low-density lipoprotein, high-density lipoprotein) and health outcome indications (e.g. quality of life, morbidity, mortality).

Data extraction

We extracted data using data collection forms. The form was developed and then piloted on a random sample of three studies. We contacted six study authors of original studies for clarification of details or further information, of whom five responded.

Data analysis

We grouped studies according to the type of intervention used and compared outcomes across these categories. We attempted to recalculate results where the reported data allowed this, using the Stata 8.0 statistical software package.\textsuperscript{13}

Quality assessment

The four main sources of systematic bias (selection bias, performance bias, attrition bias and detection bias) were considered in the process of study assessment, as recommended by the Cochrane Reviewers' Handbook.\textsuperscript{14} An overall assessment of the studies was performed by categorizing 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).
Results

Characteristics of included studies
The search contained 4254 articles, of which nine studies met all the inclusion criteria with a combined patient population of 6069 (Fig. 2). Three of the included trials took place in primary care,15–17 two in secondary care18,19 and one in both.20 Other settings were local pharmacies,21 health maintenance organizations22 and veteran affairs medical centres23 (Table 1). The geographical settings included the USA (n = 6), Canada (n = 1) and Spain (n = 2). Of the four main classes of lipid-lowering drugs, no RCTs assessed adherence to fibrates, two RCTs to nicotinic acid/niacin drugs,18,23 three RCTs to anion-exchange resins19,20,23 and six RCTs to statins.15–17,19,21,22 Patient morbidity ranged from participants with pre-existing cardiovascular pathology or increased cardiovascular risk16,18,19 to healthy patients with high cholesterol levels15,17,20 or both.21–23 Follow-up time was generally short, ranging from 2 to 24 months.

Methodological quality
Few of the reported studies provided sufficient details on study design to assess methodological quality with confidence. None of the RCTs met all the methodological quality criteria and were therefore assessed as having moderate to high risk of bias. Blinding patients to the intervention they were receiving was not possible in this particular setting. Blinding of the health carer/doctor in order to avoid systematic differences in the care provided (performance bias) was attempted in two trials.15,19 Subgroup analyses, cluster randomized and cross-over designs were used without applying relevant statistical analysis.18,21

Adherence and lipid outcomes
There was substantial between-study heterogeneity in terms of population, class of lipid-lowering drugs used, measurement of adherence and length of follow-up, making pooling of data inappropriate. Baseline mean adherence levels were generally high (>80%) but fell substantially (<40%) at longer term follow-up (6–24 months). Physiological indicators of patient compliance such as serum lipids were only reported in five out of nine trials (Table 1).15,17–20

Simplification of drug regimen (two RCTs). No consistent pattern emerged in terms of improving adherence. Reducing drug intake from four times to twice daily improved adherence and serum lipids; mean medication intake was increased by 11% and mean total

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**Table 1**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Setting</th>
<th>Lipid-Lowering Drugs</th>
<th>Adherence Outcome</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Primary care</td>
<td>Fibrates</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Secondary care</td>
<td>Nicotinic acid/niacin</td>
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<td></td>
<td></td>
<td>Local pharmacies</td>
<td>Anion-exchange resins</td>
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<td></td>
<td></td>
<td>Health maintenance organizations</td>
<td>Statins</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Veteran affairs medical centres</td>
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**Figure 2**  Progress of selecting papers through the review (search November 2005)
serum–cholesterol was decreased significantly by 14 mg/dl.\textsuperscript{18} Conversely, drug modification by administering cholestyramine bar instead of powder to make intake easier was not associated with improved adherence levels or improved lipid levels.\textsuperscript{20}

**Patient information and education (two RCTs).** There were improved effects on adherence in both RCTs. Videotapes, booklets and newspapers handed out by the local pharmacist followed by educational newsletters sent via post increased adherence by 13%.\textsuperscript{21} The effect of the intervention was more substantial in the subgroup of patients taking newly initiated statins compared to those on repeat medication.\textsuperscript{21} Another study applied a less personal approach by simply sending videotapes to members of a health maintenance organization, increasing adherence rates only slightly and non-significantly.\textsuperscript{22} In both these trials, no data on effect of adherence on lipid levels were reported.

**Intensified patient care (four RCTs).** Intensified patient care in the form of telephone reminder as well as written material was associated with improved adherence in all four RCTs, with two RCTs reaching statistical significance.\textsuperscript{17,19} There was a positive but non-significant trend towards improvement in lipid levels in two studies.\textsuperscript{17,19}

**Complex behavioural approach.** In a single RCT where participants attended small group training re-enforced with postal information, a non-significant improvement in adherence occurred, with a significant decrease in triglycerides of 30 mg/dl.\textsuperscript{15}

**Discussion**

**Principal findings**

This systematic review shows that there have been few RCTs that have examined the impact of adherence-enhancing interventions for lipid-lowering drugs. There is some evidence that intensified patient care, in the form of telephone reminders backed up with written information, improves patient adherence. The effect of these interventions appears to be greater on follow-up >6 months when adherence levels fall. This is not surprising as initially high adherence levels may reduce effect sizes and lead to underestimation of the intervention effect.

There is a paucity of evidence concerning the longer term effectiveness and cost-effectiveness of adherence-enhancing interventions and incomplete evidence concerning their effects on serum lipid levels. Treatment with statins was not associated with higher adherence levels (Table 2). In the context of observational research suggesting that statins are better tolerated than other classes of lipid-lowering drugs, this was an unexpected finding most likely related to the relatively small number of trial participants.

**Context**

The indication for prescribing lipid-lowering drugs has changed substantially over the last 10 years.\textsuperscript{2} With evidence to suggest that effectiveness of statins occurs irrespective of initial lipid level, greater numbers of people are being actively prescribed lipid-lowering agents. Observational studies have shown that adherence to lipid-lowering drugs is poor, with patients taking their medication only 60% of the time in a 1-year period.\textsuperscript{24} There is strong evidence that adherence diminishes over time in patients who are being treated as part of a primary or secondary prevention strategy.\textsuperscript{10,12} The consequence of inadequate adherence to lipid-lowering therapy is substantial. In secondary prevention, inadequate adherence is associated with an increase in recurrent myocardial infarction and all cause mortality.\textsuperscript{8} For these reasons, it is important that effective and cost-effective strategies to improve adherence are found for primary and secondary prevention of cardiovascular disease in the community.

**Limitations**

The difficulty in measuring adherence accurately and reliably is a significant limitation for any systematic review that seeks to assess the effectiveness of different adherence-enhancing strategies. Agreement on concerning the ‘gold standard’ for adherence measurement is difficult to find, with different measurement methods having different strengths and weaknesses.\textsuperscript{25} 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.\textsuperscript{26–28} Serum lipid measurement seems more reliable, but does not provide comparable data due to the impact of different medication and dosages on efficacy of lipid lowering.\textsuperscript{29} As a result, the relationship between lipid levels and adherence is difficult to establish. A further limitation of this review is the relatively short duration of follow-up in all but one of the included RCTs. Observational studies have shown that adherence to lipid lowering falls substantially over time: the effectiveness of adherence-enhancing interventions may be more worthwhile during longer periods of follow-up.

**Future research**

The majority of interventions described in this review focus on only one or two aspects of adherence. However there are many factors—knowledge, health beliefs, risk perception, memory, side effects of medication, costs of medication and inconvenience that influence adherence to drugs.\textsuperscript{3} The phenomenon of adherence is complex and it would seem reasonable for interventions to address this complexity with
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Population; Drug class; N; Duration of FU</th>
<th>Intervention</th>
<th>Adherence measure</th>
<th>Outcome (1); mean adherence (%); intervention versus control difference</th>
<th>Outcome (2); lipid levels (net change in mg/dl)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simplification of drug regimen</td>
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<tr>
<td>Brown et al.</td>
<td>Trial subgroup of FAT study, patients at high-risk CHD, mean age = 49, male = 100% Drug class: nicotinic acid N = 29, FU = 8 months</td>
<td>Niacin twice daily versus niacin four times daily</td>
<td>Pill count</td>
<td>96% versus 85%; +11%; P = 0.01</td>
<td>TC 14↓, P &lt; 0.05; LDL 13↓, P &lt; 0.005; HDL 4↓, P &lt; 0.05; TRG 12↑, ns; LDL/HDL 0.17, P &lt; 0.02 (provided by author)</td>
<td>Cross-over design. Effect ‘blurred’ by two additional drugs, lovastatin bd or colestipol bd in intervention and control groups, respectively. No baseline adjustment in serum lipid levels.</td>
</tr>
<tr>
<td>Sweeney et al.</td>
<td>Ambulatory care, primary prevention patients, age = 55.3 versus 55.5, male = 49% versus 44% Drug class: anion exchange resins N = 83, FU = 2 months</td>
<td>Cholestyramine bar versus cholestyramine powder</td>
<td>Pill count</td>
<td>93% versus 95%; –2%; P = 0.47</td>
<td>No between-group difference for all lipids measured</td>
<td>Short duration of FU. Losses to FU not reported. No power calculations reported. Between-group comparison adjusted for baseline levels.</td>
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<tr>
<td>Patient information and education</td>
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<tr>
<td>Poston et al.</td>
<td>Local pharmacies (n = 26 versus n = 28); primary and secondary prevention; patients on statins, new or long term; cluster randomized trial based in local pharmacies; age and gender not reported Drug class: statin N = 455, FU = 9 months</td>
<td>Pharmacist-mediated videotape, information and booklet versus no intervention</td>
<td>Prescription refill records</td>
<td>(i) New patient subgroup: 92% versus 79%, +13%; P &lt; 0.01 (ii) Repeat patient subgroup: 92% versus 91%, +1%, P &gt; 0.05</td>
<td>Not reported</td>
<td>Clustering is not adjusted for in analysis, which might lead to overestimation of adherence effects. FU phone calls also in control group with possibility of contamination. Losses to FU in control group not clearly stated. Only subgroup analysis comparison reported. No standard deviations reported.</td>
</tr>
<tr>
<td>Powell and Edgren</td>
<td>Members of HMO on statins, age and gender not reported Drug class: statin N = 568, FU = 3–9 months</td>
<td>Videotape sent via post versus no contact</td>
<td>Prescription refill records</td>
<td>73% versus 70%; +3%; P = 0.19</td>
<td>Not reported</td>
<td>Intervention group was blind to trial outcome of adherence.</td>
</tr>
</tbody>
</table>
Intensified patient care
Faulkner et al.\textsuperscript{19} Ambulatory care patients post-cardiac surgery, mean age = 64 versus 61, male = 53\% versus 60\% Drug class: statin and anion exchange \textit{N} = 30 FU = 3 and 24 months

Weekly phone call by pharmacist for 12 weeks emphasizing prevention versus usual care including dietary advice and drug instructions

(i) Short-term: 3 months, pill count
(ii) Long term: 24 months, script refill record

(i) Short-term FU—statin: 88\% versus 86\%, +2\%, \textit{P} > 0.05; colestipol: 90\% versus 88\%, +2\%, \textit{P} > 0.05
(ii) Long-term FU—statin: 63\% versus 39\%, +24\%, \textit{P} < 0.05; colestipol: 48\% versus 23\%, +25\%, \textit{P} < 0.05

Small RCT. Error in table underestimates effect of intervention on TRGs. Different measures of adherence used at FU. Different classes of lipid-lowering drugs reported separately.

Guthrie\textsuperscript{16} Community based (primary care 90\%); high risk for MI; mean age = 58 years; male = 48\% Drug class: statin \textit{N} = 4548, (recruited \textit{N} = 13 100) FU = 6 months

Telephone and early postal reminder versus usual care including late postal reminders

Self-reported adherence 80\% versus 77\%; +3\%; \textit{P}-value not reported

Not reported High dropout rate (response rate 35\%). No losses to FU reported. No SD reported.

Marquez-Contreras et al.\textsuperscript{17} Primary prevention clinics in Spain started on a statin; age = 59 versus 56; male = 53\% versus 56\% Drug class: statin \textit{N} = 126, FU = 6 months

Three standardized phone calls at 1 week, 2 and 4 months versus usual care with FU at 3 and 6 months

Pill count 93\% versus 84\%; +9\%; \textit{P} < 0.01

TC 31.6 fl, \textit{P} < 0.005; LDL 27.6 fl, \textit{P} = 0.001; HDL 4.7 fl, ns; TRG 18.3 fl, ns

Low dropouts (9\%). Mean number of patients who required intervention in order to avoid non-adherence was 3.4. Significant reduction of TC and LDL. Inconsistency in patient numbers. Adherence rates in this study only include patients having remained on the medication not including patients having discontinued their medication

Scheckman et al.\textsuperscript{23} Primary Care; Primary and Secondary Prevention; Veteran Affairs Medical Centre; age = 59 versus 62 (niacin); mostly male Drug class: nicotinic acid and anion exchange \textit{N} = 40 (cholestyramine), \textit{N} = 80 (niacin) FU = 2 and 6 months

Telephone contacts to encourage drug continuation (5 in first month) versus usual care including oral and written information

(i) Short term: 2 months, script refill records
(ii) Long term: 6 months, self-report of discontinuation rates

(i) Short-term FU—cholestyramine: 88\% versus 82\%, +6\%, \textit{P} = 0.32; niacin: 90\% versus 84\%, +6\%, \textit{P} = 0.07
(ii) Long-term FU—cholestyramine: 48\% versus 39\%, +9\%, \textit{P} = 0.17; niacin: 29\% versus 34\%, -5\%, \textit{P} < 0.87

Not reported

Single blinding attempted. Surprise pill count increases reliability. Short FU. Significant reduction in TRG. Only final endpoints compared, not adjusted for baseline.

Complex behavioural approach
Marquez-Contreras et al.\textsuperscript{13} Primary care; new onset medication; primary prevention (mostly); mean age = 56 versus 56; male = 35\% versus 41\%
Drug class: statin \textit{N} = 108, FU = 4 months

Small group training followed by postal information package versus usual GP care including verbal and written information

Pill count over 4 months (surprise pill counts in patients homes) 89\% versus 84\%; +5\%; \textit{P} = 0.09

TC 7.5 fl, ns; LDL 5.2 fl, ns; HDL 2.1 fl, ns; TRG 30 fl, \textit{P} = 0.002

FU: follow-up. TC: total cholesterol. LDL: low-density lipoprotein. HDL: high-density lipoprotein. TRG: triglyceride.

FU: follow-up. TC: total cholesterol. LDL: low-density lipoprotein. HDL: high-density lipoprotein. TRG: triglyceride.
TABLE 2  Adherence rates to classes of medication in control groups of trials

<table>
<thead>
<tr>
<th>Statins</th>
<th>Niacin, nicotinic acid</th>
<th>Anion exchange resins, bile acid sequestrants</th>
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<tbody>
<tr>
<td>Short-term adherence (%)a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>83.8b</td>
<td>84c</td>
<td>82c</td>
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<tr>
<td>86d</td>
<td></td>
<td>88e</td>
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<tr>
<td>94.8f</td>
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<tr>
<td>Long-term adherence (%)f</td>
<td></td>
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<tr>
<td>39g</td>
<td>34h</td>
<td>23d</td>
</tr>
<tr>
<td>70p</td>
<td></td>
<td></td>
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<tr>
<td>77.4j</td>
<td>85i</td>
<td>39k</td>
</tr>
<tr>
<td>79.2l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>84.4k</td>
<td></td>
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</tbody>
</table>

aLess than 6 months.

bMarquez-Contreras et al.15
cSchechtman et al.23
dFaulkner et al.15, 19
eSweeney et al.20
f6 months and more.
gPowell and Edgren, 22
hBrown et al. 18
iGuthrie, 16
jPoston et al.21
kMarquez-Contreras et al.17

There is a more patient-centred approach.2,30 Patients’ beliefs and preferences need to be acknowledged and incorporated into adherence-enhancing interventions.3 A combination of strategies including information, reminding, adherence reinforcement and emphasis on the patient’s perspective might lead to more effective adherence-enhancing strategies. In terms of lipid-lowering drug class, the main focus should be on statins as they have been shown to be the most potent lipid-lowering drugs.2 Other important aspects for future studies are that they include valid methods for measuring adherence, assess the effect on serum lipid levels and follow-up patients for a minimum of ≥12 months. Economic evaluation of the proposed intervention should also be performed.

Conclusion
In the context of increased prescribing of statins and changing indications for primary prevention, the issue of adherence to lipid-lowering drugs is an important public health issue. Evidence concerning effectiveness of adherence-enhancing strategies is sparse. Intensified patient care in the form of telephone reminders backed up with written information appears promising but requires further evaluation in terms of its effectiveness and cost effectiveness.

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Declaration
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Conflicts of interest: none.
Contributions: AS obtained funding for the review, designed, coordinated and wrote the review. She was responsible for data collection and interpreting of the data. KS conceived the idea for the review and was involved in review design, writing of the protocol, data extraction, data interpretation and commented on successive drafts of the manuscript. TF was involved with developing the protocol, interpreting the data, commenting on the included studies and successive drafts of the manuscript.

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1 WHO. Cardiovascular death and disability can be reduced more than 50 percent. http://www.who.int/mediacentre/releases/pr83/en/ (accessed on November 17, 2002).
Adherence to lipid lowering medication


