Dose-response characteristics of cholesterol-lowering drug therapies: implications for treatment

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Authors' objectives
To evaluate the effectiveness and toxicity of lipid-lowering agents at various doses in the treatment of hypercholesterolaemia, and to evaluate the effectiveness of drug combinations.

Searching
MEDLINE was searched from January 1975 to November 1995 using the subject headings 'hyperlipidemia' or 'hypercholesterolemia' and one of the cholesterol-lowering agents, i.e. statins (lovastatin, pravastatin, simvastatin, fluvastatin), bile acid sequestrants (including cholestyramine and colestipol), or niacin.

Study selection
Study designs of evaluations included in the review
Controlled clinical trials using at least two doses of a cholesterol-lowering drug as monotherapy for hypercholesterolaemia, or trials using at least two of the three classes of lipid-lowering drugs (statins, sequestrants, and niacin). The trials had to include at least 10 adult patients per treatment group, with a treatment period of at least 1 month, drug doses which did not depend on whether target lipid levels were achieved, and adequate description of study design. Trials comparing combination treatments had to report LDL cholesterol levels when the two drugs were used separately and in combination.

Specific interventions included in the review
Treatment for hypercholesterolaemia using statins (lovastatin, pravastatin, simvastatin, fluvastatin), bile acid sequestrants (cholestyramine, colestipol), or niacin (immediate- and sustained-release). Both monotherapy and combination therapies were considered.

Participants included in the review
People with hyperlipidaemia or hypercholesterolaemia. No patient criteria are given, although patients with triglyceride levels greater than 2.8 to 4.5 mmol/L at baseline, or less than 2.5 mmol/L at study entry, were generally excluded from the primary studies.

Outcomes assessed in the review
Reduction in low-density lipoprotein (LDL) cholesterol level, and high-density lipoprotein (HDL) cholesterol level (for niacin monotherapy).

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The authors do not report the method used to assess validity, or how the validity assessment was performed.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.
Methods of synthesis
How were the studies combined?
The studies were combined in a narrative review. To estimate the effect of two different drugs used in combination, it was assumed that both act independently and the effect is additive.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

Results of the review
Dose-response monotherapy using: statins, 15 trials (approximately 3,573 patients); sequestrants, 6 trials (approximately 196 patients); and niacin, 3 trials (approximately 142 patients). Combination therapy: 6 trials (215 patients). Low-dose combination versus higher-dose monotherapy: 3 trials (98 patients).

Statins: increasing the dose of each statin to more than 20 mg produces only small incremental reductions in the LDL cholesterol level. The effectiveness of the statins does not increase proportionally with dose and approximately two thirds of the expected maximum response can be expected with only one quarter of the highest dose.

Bile acid sequestrants: sequestrants have a non-linear dose-response relation. Two to 3 scoops daily reduce LDL cholesterol levels by 15 to 25%. Three scoops provided three-quarters of the lowering effect that was achieved by 6 scoops. Higher doses (4 to 6 scoops daily) are associated with substantial adverse gastrointestinal side-effects.

Niacin: the dose-response curve for niacin (both immediate- and sustained-release), in terms of reduction in the LDL cholesterol level, is linear and directly proportional to the dose used. Reductions of 15% in LDL cholesterol levels are achieved with daily doses of at least 1.5 g. The majority of the elevation in HDL cholesterol levels occurs with 1.5 g of niacin. Immediate-release niacin increased HDL cholesterol levels more effectively than sustained-release. Niacin is associated with significant toxicity, but relatively little is known about the relationship between dose and adverse effects.

Combination therapy: 3 studies evaluating combination therapy with statins and niacin found that the predicted LDL cholesterol level reduction was similar to that which would be expected from the use of either drug alone.

Three studies evaluating combination therapy with statins and sequestrants found the LDL cholesterol reductions to be additive.

Low-dose combination therapy versus higher-dose monotherapy: combinations of low-dose sequestrants and statin produce reductions in LDL cholesterol levels greater than or equal to higher doses of either drug used alone. Low-dose combination therapy minimises toxicity.

Authors’ conclusions
The non-linear dose-response relationship of statins, bile acid sequestrants and niacin, and their additive LDL cholesterol-lowering effect when used together, suggest a strategy for treating hypercholesterolaemia that may optimise effectiveness while minimising adverse effects and cost.

CRD commentary
It was difficult to evaluate this review as the methodology was not described clearly. The search was relatively limited, with attention focused on one computerised database, and there was no attempt to identify unpublished studies. It was also unclear whether non-English language publications were considered. Insufficient detail was provided about the primary studies included in the review, in particular the study participants and their characteristics. Thus, it is difficult to draw conclusions about the generalisability of the results of the review.

The validity of the included studies was not discussed, and it was unclear how decisions about the relevance and validity of studies were made.
The authors discussed the use of diet, but provided very little information about the dietary studies to which they were referring. Similarly, they discussed the costs of treatment without providing any information. It is unclear whether the treatment strategies the authors recommend follow directly from the evidence.

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