Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials


CRD summary
This review evaluated the effects of five categories of drugs, singly and in combination, on blood pressure and adverse events. The authors concluded that combination low-dose treatment increased efficacy and reduced adverse effects compared with a single agent at a higher dose. The conclusions depended on a number of assumptions and should be treated with caution.

Authors' objectives
To determine the average reduction in blood-pressure (BP), prevalence of adverse effects, and reduction in risk of stroke and ischaemic heart disease events produced by the five main categories of BP-lowering drugs according to dose, singly and in combination.

Searching
MEDLINE (from 1966 to 2000, extended to 2001 for angiotensin-II receptor antagonists because these trials are the most recent), the Cochrane Controlled Trials Register and ISI Web of Science were searched. Full details of the search strategy are available on the Wolfson Institute's website (see Other Publications of Related Interest). Here the authors stated that they searched all relevant citations in the reports of the trials identified and in review articles, and asked pharmaceutical companies to identify trials of drugs that they manufactured.

Study selection
Study designs of evaluations included in the review
The review included randomised placebo-controlled trials. Both crossover and parallel studies were included in the review. Studies of less than 2 weeks' duration were excluded.

Specific interventions included in the review
The inclusion criteria specified any BP-lowering drug from the five main classes of hypotensive agents. In the included studies, the interventions were 53 BP-lowering drugs, from the following five classes: thiazides, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists and calcium-channel blockers. Details of the specific drugs and standard daily doses of each drug are available on the Wolfson Institute's website. See Web Address at end of abstract. The comparator was placebo. Combinations of two BP-lowering drugs were also assessed. Studies with no placebo group, with titrated doses, or that tested drugs only in combination were excluded.

Participants included in the review
The participants included in the review were patients undergoing treatment with hypotensive agents. Most of the participants had high BP, but trials of people with nonvascular conditions were also included. There were no exclusion criteria in relation to the age of the included participants. Trials of patients with heart failure, acute myocardial infarction, or other cardiovascular disorders were excluded. Trials in which most of the participants were black were also excluded. The median age of the included participants was 53 years (90% range: 43 to 68), the median systolic BP was 154 (90% range: 139 to 170) and the median diastolic BP was 97 (90% range: 87 to 106).

Outcomes assessed in the review
The outcomes to be assessed were placebo-adjusted reductions in the systolic and diastolic BP, according to dose, expressed as a multiple of the standard dose. BP was recorded sitting or supine. In the included studies, the results were expressed as averages of the peak and trough BP readings over 24 hours. The prevalence of adverse effects was reported. This was expressed as the number of participants showing at least one attributable effect, as well as the number stopping treatment because of adverse effects. Headache was excluded as an adverse event, but metabolic
effects such as changes in serum cholesterol, potassium, glucose and uric acid were included.

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

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors stated that two authors extracted the data, but did not state how they performed the data extraction. The authors reported on doses which were standard, half standard and twice standard. Standard doses of each drug were specified as the 'usual maintenance dose' in reference pharmacopoeias.

Methods of synthesis
How were the studies combined?
The authors stated that they fitted random-effects regression models (separately for systolic and diastolic BP) to estimate the change in BP in each treatment arm (treated minus placebo) according to category of drug and dose, weighted by the inverse of its variance. Placebo-adjusted estimates of the BP-lowering effect by dose were used to indirectly compare drug categories.

How were differences between studies investigated?
The authors did not state a method for assessing any differences between the studies. However, they noted that within each of the five categories the average reductions in systolic and diastolic BP recorded showed statistically-significant heterogeneity across trials. The authors also stated that parallel and crossover trials yielded similar results, so these were combined. All five categories of drugs produced similar reductions in BP.

Results of the review
A total of 354 trials were included in the review; these involved 791 treatment groups testing different drugs or different doses of the same drug. The trials included 39,879 patients who received treatment and 15,817 participants who received placebo. The numbers of participants who received treatment and placebo, respectively, were as follows: thiazides, 4,502 and 2,636; beta-blockers, 5,189 and 2,701; ACE inhibitors, 9,350 and 4,712; angiotensin II receptor antagonists, 12,840 and 5,100; and calcium-channel blockers, 7,998 and 3,976. Fifty studies compared drugs from two categories separately and in combination.

The average reductions in systolic BP over 24 hours produced by standard doses of the five drug categories were 8.8 mmHg (95% confidence interval, CI: 8.3, 9.4) for thiazides, 9.2 mmHg (95% CI: 8.6, 9.9) for beta-blockers, 8.5 mmHg (95% CI: 7.9, 9.0) for ACE inhibitors, 10.3 mmHg (95% CI: 9.9, 10.8) for angiotensin II receptor antagonists, and 8.8 mmHg (95% CI: 8.3, 9.2) for calcium-channel blockers. Half standard doses compared with standard doses produced only relatively small changes in the outcomes: the proportional reductions in effect for each drug category were 16, 20, 19, 24 and 33%, respectively.

The reduction in diastolic BP for a standard dose of each drug category was 4.4 mmHg (95% CI: 4.0, 4.8) for thiazides, 6.7 mmHg (95% CI: 6.2, 7.1) for beta-blockers, 4.7 mmHg (95% CI: 4.4, 5.0) for ACE inhibitors, 5.7 mmHg (95% CI: 5.4, 6.0) for angiotensin II receptor antagonists, and 5.9 mmHg (95% CI: 5.6, 6.2) for calcium-channel blockers. For half standard doses compared with standard doses, the proportional reductions in effect for each drug category were 16, 16, 21, 21 and 34%, respectively.

The prevalence of adverse events attributable to treatment with a standard dose of each drug category was 9.9% (95% CI: 6.6, 13.2) for thiazides, 7.5% (95% CI: 4.0, 10.9) for beta-blockers, 3.9% (95% CI: 0.5, 8.3) for ACE inhibitors, 0% (95% CI: 5.4, 5.4) for angiotensin II receptor antagonists, and 8.3% (95% CI: 4.8, 11.8) for calcium-channel blockers. Half standard doses resulted in a reduced prevalence of adverse events: thiazides, 2.0% (95% CI: -2.2, 6.3);
beta-blockers, 5.5% (95% CI: 0.3, 10.7); ACE inhibitors, 3.9% (95% CI: -3.7, 11.6); angiotensin II receptor antagonists, 1.8%, (95% CI: -10.2, 6.5); calcium-channel blockers, 1.6% (95% CI: -3.5, 6.7). The percentage of people with symptoms attributable to treatment that were sufficient to stop taking the tablets, were also reported.

There was an additive effect of taking two different classes of drug together for 6 of the 10 possible combinations: average cumulative reduction in BP was 14.6 mmHg systolic (standard error 0.5) and 8.6 mmHg diastolic (standard error 0.4). No trials reported on the cumulative effect of three drugs, but the authors estimated what the effect would be. Adverse metabolic effects were negligible at half standard doses.

Cost information
The authors did not perform any economic analyses, but did note the cost per standard dose of treatment. They stated that the cheaper drugs within each category were as effective as the more expensive ones.

Authors' conclusions
Compared to treatment with a single agent at a higher dose, combination low-dose drug treatment increased efficacy and reduced adverse effects. The authors noted that no category of drug was materially more effective than another. The efficacy of drugs in combination was additive, whereas the prevalence of adverse effects was less than additive.

CRD commentary
This was a well-written review. There were insufficient details in the abridged paper to critique the methodology used, but further details are available on the BMJ website (full version of the paper; see Web Address at end of abstract) and the Wolfson Institute's website (see Other Publications of Related Interest). The search strategy was comprehensive, although the MEDLINE search was restricted to English language publications. The exclusion of studies published in other languages may have biased the results. The authors’ decision to exclude trials in which the majority of the participants were black means that the generalisability of the results will be limited to those populations studied. However, insufficient details of the participants in the included studies were given. The authors did not report any method for analysing the validity of the studies, so there is no information on the quality of the included data.

The results which the authors presented were based on combined results from parallel and crossover studies, and indirect comparisons of standard and half standard doses. These results may not be as robust as those arising from a mega-trial or standard meta-analysis. The assumptions made, such as the use of variance estimated for 45 trials and the linear fit of the regression model, were not well justified.

The authors’ conclusions were extrapolated from the presented results, rather than following logically. For example, the conclusions that no category of drug is more effective than another was based on indirect comparisons. The authors concluded that combinations of three drugs will act additively, but this is an assumption based on the observation that combinations of two drugs do so.

There is a potential conflict of interest in the review: the authors have submitted a patent application for a pill combining more than two medications.

Implications of the review for practice and research
Practice: The authors stated that low-dose combination treatment should be used as a first option in lowering BP, to maximise efficacy and minimise adverse effects. The use of BP-lowering drugs should be determined by a person's overall level of risk rather than the BP alone.

Research: The authors did not state any implications for further research.

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**Other publications of related interest**
These additional published commentaries may also be of interest. Linden W. Review: lower-dose combination antihypertensive therapy is preferable to standard-dose single-drug therapy. ACP J Club 2004;140:4. Bazian Ltd. Low dose combination treatment increases efficacy of blood pressure lowering drugs and reduces adverse effects. Evidence-based Healthcare 2004;8:45-7.

Additional data relating to this study are available on the following website: http://www.smd.qmul.ac.uk/wolfson/bpchol (accessed February 2004).

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