Fixed-dose combinations improve medication compliance: a meta-analysis
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CRD summary
This review found that fixed-dose combination medications increase medication compliance, compared with free-drug regimens, in patients with chronic conditions. Although the data appear to support these conclusions, they should be interpreted with some degree of caution because of limitations in the search and a failure to assess study quality.

Authors' objectives
To determine the efficacy of fixed-dose combination medications in improving patient compliance with drug regimens.

Searching
MEDLINE was searched from 1966 to November 2005; the search terms were reported. The reference lists of retrieved articles were also examined. The search was limited to studies published in English in peer-reviewed journals.

Study selection
Study designs of evaluations included in the review
No inclusion criteria were specified for the study design. The review included randomised controlled trials (RCTs) and retrospective database analyses.

Specific interventions included in the review
Studies that compared fixed-dose combination medications with free-drug combination medications were eligible for inclusion. Studies in the review compared fixed-dose combinations of medications with the same medications given separately. They included treatments for tuberculosis (TB) (isoniazide and rifampicin with or without pyrazinamide), human immunodeficiency virus (HIV) (lamivudine with zidovudine), hypertension (amlodipine with benazepril; lisinopril or enalapril with hydrochlorothiazide; angiotensin-receptor blockers with diuretic) and diabetes (glyburide with metformin).

Participants included in the review
No inclusion criteria were specified for the participants. The studies included men and women aged from 40 to 68 years with hypertension, diabetes, TB or HIV.

Outcomes assessed in the review
Studies that reported compliance with medication regimens were eligible. Compliance was defined in the review as adherence or persistence. The included studies used a range of measures of compliance, such as pill counting, questionnaires, medication possession ratios (calculated from prescription fill dates), urine testing, and persistence (continuing to take drug, fill prescriptions) or not lost to follow-up. The review also reported efficacy outcomes; these comprised sputum conversion rates and radiological improvement in patients with TB, and treatment failure in patients with HIV (viral load). The patients were followed up for a mean of 13.1 months (standard deviation 8.6 months; range: 4 months to 2 years).

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 did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The review reported numbers experiencing each outcome in the control and intervention arms of each study, with associated risk ratios (RRs) and 95% confidence intervals (CIs).
Methods of synthesis

How were the studies combined?
The studies were combined in a meta-analysis, weighted according to the inverse of the variance. Fixed-effect models were used where the results were homogeneous, and the DerSimonian and Laird random-effects model where they were not. Publication bias was assessed using the rank correlation test of Begg and the weighted regression test of Egger.

How were differences between studies investigated?
Heterogeneity among the studies was investigated visually by scanning plots of the data and statistically using the Q test (p-value of less than or equal to 0.05 was considered significant). A subgroup analysis was performed for studies of participants with hypertension. A sensitivity analysis by study design was also conducted.

Results of the review
Seven studies (n=20,242) reporting 9 comparisons were included: 3 RCTs (n=1,029) and 4 retrospective database analyses (n=19,213), two of which included two subgroup comparisons.

Compliance was significantly higher in patients receiving the fixed-dose combination than in those receiving the free-drug combination (RR for non-compliance 0.74, 95% CI: 0.69, 0.80, p<0.0001; 9 comparisons); the results were similar in studies of patients with hypertension (RR 0.76, 95% CI: 0.71, 0.81 p<0.0001; 4 comparisons, n=17,175). There was moderate evidence of heterogeneity (p=0.07). When the analysis was restricted to the 3 RCTs, the difference between the groups was no longer statistically significant (RR 0.83, 95% CI: 0.64, 1.07). When the meta-analysis was restricted to observational studies, the results were similar to those found when all studies were included, but there was significant heterogeneity (p=0.016). There was no evidence of publication bias for any of the analyses.

In term of efficacy, one RCT of patients with TB reported that sputum conversion at 8 weeks was significantly higher in the fixed-drug combination group (86.6% versus 77.7%, p<0.05). A second RCT reported no significant difference in sputum conversion or radiological improvements. The third RCT assessed treatment failure in patients with HIV and found no significant difference between the groups.

Authors' conclusions
Fixed-dose combinations decrease the risk of medication non-compliance and should be considered as a means of increasing medication compliance in patients with chronic conditions.

CRD commentary
The review question was focused, with inclusion criteria defined for the interventions and outcomes but not for the study design or participants. The search was limited and restricted to fully published studies in English, which might have resulted in some studies being missed. It is not clear whether appropriate procedures were undertaken when selecting studies for inclusion or extracting the data, thus the potential for reviewer bias and error cannot be determined. A formal quality assessment was not conducted, so the reliability of the authors’ conclusions is unclear. Relevant details of the included studies were reported. The studies were combined in a meta-analysis, which appears appropriate, and heterogeneity was evaluated using suitable methods. The authors’ conclusions appear well supported by the data presented, but limitations in the search and a failure to assess study quality mean that they should be interpreted with some degree of caution.

Implications of the review for practice and research
Practice: The authors stated that fixed-dose medication combinations should be considered in patients with chronic diseases in order to increase medication compliance, as this may translate into better clinical outcomes.

Research: The authors stated the need for further studies on the topic of compliance.

Funding
Not stated.
Bibliographic details

PubMedID
17679131

DOI
10.1016/j.amjmed.2006.08.033

Other publications of related interest
This additional published commentary may also be of interest.

Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Aged; Anti-HIV Agents /administration & dosage; Antihypertensive Agents /administration & dosage; Antitubercular Agents /administration & dosage; Chronic Disease /drug therapy; Comorbidity; Diabetes Mellitus /drug therapy /epidemiology; Disease Management; Drug Combinations; HIV Infections /drug therapy; Humans; Hypertension /drug therapy /epidemiology; Hypoglycemic Agents /administration & dosage; Middle Aged; Patient Compliance; Polypharmacy; Tuberculosis /drug therapy

AccessionNumber
12007005994

Date bibliographic record published
01/04/2008

Date abstract record published
01/12/2008

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.