Fixed-dose combination antituberculosis therapy: a systematic review and meta-analysis

Albanna AS, Smith BM, Cowan D, Menzies D

CRD summary
The authors concluded that although fixed-dose combination formulations simplified tuberculosis therapy, the current evidence did not indicate that these formulations improved treatment outcomes among patients with active tuberculosis. The authors' conclusions reflect the evidence presented and are likely to be reliable.

Authors' objectives
To evaluate the effectiveness and adverse effects of fixed-dose formulations for the treatment of patients with active tuberculosis.

Searching
Five databases including MEDLINE, EMBASE and The Cochrane Library (which included DARE) were searched for articles in any language between January 1980 and July 2011. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) or cohort studies were eligible for inclusion if they evaluated effective (as defined in paper) anti-tuberculosis treatment regimens for active tuberculosis (bacteriologically confirmed) using fixed-dose combination formulations compared with separate drug formulations. Cohort studies had to include 50 or more patients. Treatment with fixed-dose combination formulations had to include rifampin and isoniazid. Studies had to measure at least one of the outcomes of interest such as bacteriologically confirmed treatment failure or disease relapse, acquired drug resistance (based on drug sensitivity testing), and have a follow-up period of five months or more during the treatment. Secondary outcomes were bacterial conversion after two months of treatment, adverse drug reaction, patient adherence and treatment satisfaction.

Treatment regimens included isoniazid, rifampicin, pyrazinamide, streptomycin or ethambutol. Fixed-dose combination formulation included Rimactazid, Rifater, Rifinah, Svizera or Myrin P, where reported. Direct observed therapy was reported in just over half the studies. The mean age of patients ranged from 28 to 49 years. Where reported the proportion of men ranged from 57% to 100%. Studies were published between 1989 and 2011. Locations of studies included India, South Africa, China, Algeria, Singapore, Taiwan, Romania, Egypt, Switzerland, Pakistan, Philippines, Thailand and Indonesia.

Two reviewers independently selected studies for inclusion. Disagreements were resolved by a third reviewer.

Assessment of study quality
Study quality was assessed using a modified Cochrane risk of bias tool. Two reviewers independently assessed study quality.

Data extraction
Data on treatment outcomes were extracted and used to calculate risk ratios and 95% confidence intervals for comparative studies and effect sizes for non-comparative studies. Study authors were contacted for missing data where necessary. Two reviewers independently extracted data.

Methods of synthesis
Pooled risk ratios and corresponding 95% confidence intervals were calculated using a DerSimonian and Laird random-effects model. Statistical heterogeneity was assessed using $\chi^2$ and $I^2$. Moderate heterogeneity was defined as $I^2$ between 40% and 60% and substantial heterogeneity as $I^2$ greater than 60%. Where heterogeneity was moderate or significant, or where methods of ascertainment across studies were inconsistent, the outcome estimates were not pooled. Subgroup and meta-regression analyses were undertaken to assess factors influencing primary outcome results. Data from non-comparative studies were reported narratively. Publication bias was assessed using funnel plots and Egger's test.
Results of the review
Nineteen studies were included: 15 RCTs (5,630 patients), one comparative cohort and three non-comparative studies. Five RCTs reported an adequate allocation sequence, three trials reported adequate allocation concealment, 13 RCTs reported adequate follow-up completion, all studies reported non-selective outcome reporting and nine RCTs reported being free of other biases.

Compared to separate drug formulations, fixed-dose combination treatment resulted in a non-significant trend towards a higher risk of treatment failure or disease relapse (RR 1.28, 95% CI 0.99 to 1.7; 13 RCTs). There was no significant heterogeneity for this analysis ($I^2=0$).

There were no significant differences between treatment groups for acquired drug resistance (four RCTs) or adverse drug reaction (10 RCTs).

Subgroup analyses reported a significantly higher risk of treatment failure or drug relapse for fixed-dose combination treatment for patients with baseline drug-sensitive tuberculosis (RR 1.48, 95% CI 1.04 to 2.09; six RCTs) and for patients receiving self-administered therapy (RR 1.94, 95% CI 1.05 to 3.57). Multivariate regression analyses did not indicate any significant influence of publication year or study quality on the primary outcome. Other results were reported. There was no evidence of significant publication bias.

Authors' conclusions
Although fixed-dose combination formulations simplified tuberculosis therapy, the current evidence did not indicate that these formulations improved treatment outcomes among patients with active tuberculosis.

CRD commentary
The review question was clear with defined inclusion criteria. Several relevant sources were searched without language restriction which reduced potential for language bias. The authors did not appear to search for unpublished studies, but formal assessment found no evidence of publication bias. Study quality was assessed and results for individual studies were reported; study quality appeared variable. Appropriate methods to reduce reviewer error and bias were used throughout the review process. Methods of analysis appeared appropriate and reasons for heterogeneity were explored.

The authors' conclusions reflect the evidence presented and are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that the current evidence does not support the use of fixed-dose combination formulations for the purpose of improving treatment outcomes among patients with active tuberculosis.

Research: The authors stated that further research on clinical effectiveness of fixed-dose combination anti-tuberculosis formulations should utilise pragmatic trial designs to simulate real-world clinical practice while minimising confounding.

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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.