Systematic review with meta-analysis: the effects of rifaximin in hepatic encephalopathy

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CRD summary
The authors concluded that rifaximin had a beneficial effect on hepatic encephalopathy and could reduce mortality. There was potential for error and bias in the selection of trials, and there were inconsistencies between the abstract and the main text, but the remainder of the review appeared to be well conducted. Despite the caveats, the authors’ conclusion and recommendations seem reliable.

Authors' objectives
To evaluate the effects of rifaximin for patients with hepatic encephalopathy.

Searching
The Cochrane Library, MEDLINE, EMBASE, Cochrane Hepato-Biliary Group Trials Register, Science Citation Index Expanded, and other clinical trial registers were searched in April 2014; search strategies were available. Bibliographies and the proceedings of four conferences were searched manually. All corresponding authors, including pharmaceutical sponsors, were contacted. Information was sought from websites of the US Food and Drug Administration and the European Medicines Agency. There were no restrictions on language and publication status.

Study selection
Eligible for inclusion were randomised controlled trials of rifaximin for the prevention of hepatic encephalopathy, in patients with overt or minimal hepatic encephalopathy. Trials of patients with a transjugular intrahepatic portosystemic shunt (TIPS) were included, to enable sensitivity analysis.

Over half of the included trials were conducted in Italy. Most trials were of patients with cirrhosis (largely related to alcohol or viral hepatitis). Rifaximin dose ranged from 1,100mg to 1,200mg per day, and treatment lasted between five and 180 days. Control patients received placebo, a disaccharide, or another antibiotic. The primary outcomes were prevention, recovery, and improved manifestations of hepatic encephalopathy. Secondary outcomes were surrogate markers of hepatic encephalopathy (psychometric tests and ammonia levels).

The authors did not state how many reviewers selected the trials for inclusion.

Assessment of study quality
Trial quality was assessed using Cochrane criteria (sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias). Each was rated as low, unclear, or high risk of bias.

Two reviewers independently assessed quality.

Data extraction
The data were extracted by three reviewers independently, to calculate risk ratios or mean differences, with 95% confidence intervals.

Methods of synthesis
Effect sizes were combined in a random-effects meta-analysis, and 95% confidence intervals were presented. Fixed-effect analysis was conducted to test the stability of the results. Individual patient data were analysed, where available. The number needed to treat (NNT) was calculated for statistically significant primary outcomes, in trials with a low risk of bias, and confirmed in sequential analysis.

Statistical heterogeneity was assessed with $X^2$ and $I^2$. An $I^2$ of 30% to 60% was moderate; 60% to 75% was considerable; and over 75% was high. Subgroup, sensitivity, and regression analyses were conducted to explore potential sources of heterogeneity. Publication bias was assessed using funnel plots.

Results of the review
Nineteen trials (1,370 patients) were included in the review. Another trial of 75 patients with TIPS was included in the sensitivity analysis. Sequence generation and allocation concealment were adequate in 16 trials; 14 trials were double blind and had no missing outcome data. Three trials were considered to have a risk of other bias.

A statistically significant effect was found with Rifaximin for the prevention of overt hepatic encephalopathy (RR 1.36; 95% CI 1.06 to 1.65; two RCTs). The significance of this result was reduced when the trial on TIPS was included (RR 1.24, 95% CI 1.00 to 1.53; I²=50%).

Rifaximin was statistically significant for full resolution of hepatic encephalopathy (RR 1.34, 95% CI 1.11 to 1.62; 11 RCTs; I²=54%; NNT six). The significance of this result was unaltered in the sensitivity analysis including only trials with a low risk of bias. There was no evidence of publication bias.

There were statistically significant improvements in manifestations of hepatic encephalopathy (RR 1.00, 95% CI 1.00 to 1.23 – random effects; and RR 1.19, 95% CI 1.11 to 1.27 – fixed effect). The number of trials in the analysis was not reported. The statistical significance remained in the fixed-effect sensitivity analysis only. There was evidence of publication bias. Sequential analysis showed that additional information was needed to support or refute improved hepatic encephalopathy manifestation.

Rifaximin significantly reduced mortality (RR 0.64, 95% CI 0.43 to 0.94; 12 RCTs; I²=0). The sequential analysis revealed that further trials were necessary to confirm this finding.

There were no differences between Rifaximin and control for serious adverse events (13 RCTs). Where it was possible to combine data (four RCTs), the result was not statistically significant.

The results for secondary outcomes, and of further sensitivity and subgroup analyses, were reported.

**Authors' conclusions**

Rifaximin had a beneficial effect on hepatic encephalopathy and could reduce mortality.

**CRD commentary**

The review question was clear and the inclusion criteria were specified; the outcomes may have been defined after the trials were assessed. The search strategy seems to have been wide reaching, and included attempts to find all relevant trials. The trial selection process was unclear, but data extraction and quality assessment were carried out with attempts to minimise error and bias. Suitable quality assessment criteria were used, and the overall standard of trials appeared to be reasonable. The method of synthesis seemed appropriate, and various exploratory analyses were reported.

There was potential for error and bias in the selection of trials, and there were some differences in the reporting of the results between the abstract and the main text, but the remainder of the review appeared to be well conducted. Despite the caveats, the authors' conclusion and recommendations seem reliable.

**Implications of the review for practice and research**

**Practice**: The authors stated that rifaximin could be considered for the evidence-based management of hepatic encephalopathy.

**Research**: The authors stated that trials were needed to determine the effects of combining different interventions, and to identify the best treatment duration in different situations. Trials were also needed to determine if rifaximin reduced mortality, and to assess its effects on bacterial translocation, infections, and complications to cirrhosis.

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**Bibliographic details**


**PubMedID**
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.