Rifaximin versus nonabsorbable disaccharides for the treatment of hepatic encephalopathy: a meta-analysis

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CRD summary
This review concluded that rifaximin for the treatment of hepatic encephalopathy, was as effective as non-absorbable disaccharides, possibly better, with fewer side-effects. The authors' conclusions reflect the evidence presented, but small samples, some statistical heterogeneity, and limitations in the quality of the included trials, make the reliability of the findings uncertain.

Authors' objectives
To evaluate the effectiveness of rifaximin, compared with non-absorbable disaccharides, such as lactulose or lactitol, for the treatment of patients with hepatic encephalopathy.

Searching
PubMed, EMBASE, The Cochrane Library, CINAHL, and Science Citation Index were searched up to August 2012. Search terms were reported. No restrictions were placed on language and publication status. Reference lists of included studies were handsearched.

Study selection
Randomised controlled trials (RCTs) that compared rifaximin with non-absorbable disaccharides, for the treatment of patients, who were over 18 years old, were eligible for inclusion. Patients had to have the signs and symptoms of acute, chronic hepatic encephalopathy, according to Conn's modification of the Parsons Smith classification. Trials of patients who had psychiatric illnesses or whose infections were related to other conditions were excluded.

The included trials were conducted between 1993 and 2005, in South Korea, Italy, or Spain. Most of the trials were conducted in one centre. The dose of rifaximin was 1,200mg per day, and the dose of non-absorbable disaccharides ranged from 45 to 120mL per day for lactulose, and 60g per day for lactitol. Treatment lasted between seven days and three months.

Two reviewers independently screened studies for eligibility.

Assessment of study quality
Trial quality was assessed, based on the Cochrane risk of bias tool; each item was rated 'yes', 'no', 'unclear', or 'not available'.

Two reviewers independently assessed trial quality and any disagreements were resolved by discussion.

Data extraction
The data were extracted to calculate relative risks, weighted mean differences, and their 95% confidence intervals.

Two reviewers independently extracted these data; disagreements were resolved by discussion.

Methods of synthesis
Pooled relative risks, weighted mean differences, and 95% confidence intervals were calculated using a random-effects model. The heterogeneity between the trials was assessed by the DerSimonian and Laird Q statistic (p<0.1).

Sensitivity analyses were performed for different ethnicity, and for chronic and acute stages of hepatic encephalopathy. Publication bias was investigated using funnel plots.

Results of the review
Eight RCTs were included in the review (407 patients). Five trials described randomisation, and six described allocation concealment. Patients were blinded to treatment in all trials, but only three trials blinded the observers. None of the
trials reported their handling of missing data and drop-out rate. The funnel plots suggested the presence of publication bias.

The meta-analysis showed no significant difference between rifaximin and non-absorbable disaccharides, in their efficacy for treating hepatic encephalopathy, serum ammonia levels, mental status, and asterixis (flapping tremor).

Rifaximin was superior to non-absorbable disaccharides in electroencephalogram response (WMD -0.21, 95% CI -0.34 to -0.09; I²=0%; two RCTs), and grades of portosystemic encephalopathy (WMD -2.30, 95% CI -2.78 to -1.82; I²=60%, two RCTs). Compared with non-absorbable disaccharides, rifaximin produced lower rates of diarrhoea (RR 0.11, 95% CI 0.04 to 0.31; I²=48%, five RCTs) and abdominal pain (RR 0.34, 95% CI 0.14 to 0.83; I²=33%, six RCTs).

Sensitivity analyses showed that ethnic differences and the presence of acute hepatic encephalopathy did not influence the efficacy of rifaximin, but there was a statistically significant difference favouring rifaximin in the treatment of chronic hepatic encephalopathy (RR 7.6, 95% CI 1.87 to 30.78).

Authors' conclusions
Rifaximin for the treatment of hepatic encephalopathy, was as effective as non-absorbable disaccharides, possibly better for some outcomes, with fewer adverse events.

CRD commentary
The review question and inclusion criteria were clear. The search covered a range of published and unpublished studies and no language restrictions were applied, minimising the risk of publication and language bias. Attempts were made to minimise reviewer error and bias, in the review process. Trial quality was assessed, using appropriate criteria. A reasonable amount of information on the individual trials was provided. Appropriate methods were used to pool the data and perform the sensitivity analyses. Statistical heterogeneity was assessed and moderate to high heterogeneity was found.

The authors' conclusions reflect the evidence presented, but small samples, some statistical heterogeneity, and limitations in the quality of the included trials, make the reliability of the findings uncertain.

Implications of the review for practice and research
Practice: The authors stated that rifaximin should be used as a second treatment option, after cheaper non-absorbable disaccharides, particularly for patients with severe adverse events on disaccharides.

Research: The authors stated that more larger RCTs were needed to assess the safety of rifaximin, including its tolerance, toxicity, bacterial resistance, and mycotic infection.

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