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RIFAXIMIN VS. LACTULOSE FOR THE MANAGEMENT OF HEPATIC ENCEPHALOPATHY: A SYSTEMATIC REVIEW

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PURPOSE / OBJECTIVES

Hepatic encephalopathy (HE) is a debilitating neuropsychiatric complication of liver failure, resulting from the accumulation of gut-derived toxins, particularly ammonia. Lactulose and rifaximin are two cornerstone therapies with distinct mechanisms of action: lactulose reduces intestinal ammonia absorption, whereas rifaximin targets the gut microbiota to decrease ammonia production. This systematic review aims to evaluate and compare the efficacy, safety, and clinical outcomes of rifaximin and lactulose, individually and in combination, for the treatment and prevention of HE.

MATERIAL & METHODS

A comprehensive literature search was performed across PubMed, Embase, and the Cochrane Library for studies published up to December 2024. Eligible studies included randomized controlled trials (RCTs) and observational studies that evaluated the use of rifaximin, lactulose, or their combination in adult patients diagnosed with hepatic encephalopathy. The primary outcomes analyzed were symptom resolution, prevention of recurrence, mortality, and treatment-related safety. A total of 27 studies, encompassing 3,526 patients, met inclusion criteria. Data were extracted and synthesized, and study quality was assessed using the Cochrane Risk of Bias tool and the GRADE framework to ensure methodological rigor

RESULTS

Rifaximin Monotherapy:
Rifaximin demonstrated non-inferior efficacy to lactulose in both resolution of HE symptoms and prevention of recurrence. A pivotal RCT involving 299 patients showed that rifaximin significantly reduced recurrence rates by 52% over a 6-month period compared to placebo ($p<0.001$).

Combination Therapy (Rifaximin + Lactulose):
The combination of rifaximin and lactulose was superior to lactulose monotherapy. Pooled results from 14 studies indicated a statistically significant improvement in HE resolution rates (Relative Risk: 1.30, 95% Confidence Interval: 1.10–1.53, $p=0.002$) and a 30% reduction in the risk of recurrence.

Safety:
Rifaximin was generally well-tolerated, with fewer gastrointestinal side effects compared to lactulose. The combination therapy also had a lower rate of adverse events relative to lactulose monotherapy.

Mortality:
There was no statistically significant difference in all-cause mortality between rifaximin and lactulose monotherapies. However, combination therapy demonstrated a trend toward reduced mortality.

Combination therapy with rifaximin and lactulose is more effective than lactulose alone in managing hepatic encephalopathy, improving symptom resolution, reducing recurrence, and lowering adverse events.
Rifaximin is well-tolerated and may be especially valuable for patients with recurrent HE or lactulose intolerance.

RESULTS

Figure 1

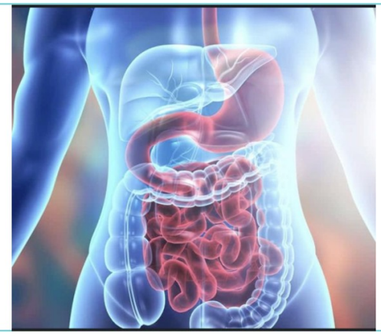

Table 1

Treatment	Symptom Resolution	Recurrence Reduction	Adverse Effects	Mortality
Lactulose Monotherapy	Moderate	Moderate	Higher GI side effects	Baseline
Rifaximin Monotherapy	Comparable to lactulose	52% decrease vs. placebo	Fewer GI side effects	No significant difference
Combination Therapy	Significantly improved	30% decrease vs lactulose	Least overall	Trend toward reduction

SUMMARY / CONCLUSION

Rifaximin and lactulose are both effective treatment options for hepatic encephalopathy. While each monotherapy provides clinical benefit, combination therapy offers superior outcomes in terms of symptom resolution, recurrence prevention, and overall safety profile. Rifaximin's favorable tolerability and added efficacy make it an ideal adjunct to lactulose in appropriate patients. However, due to cost considerations, rifaximin may be best reserved for individuals with recurrent HE or those who cannot tolerate lactulose. These findings support a complementary treatment strategy using both agents to optimize the management of hepatic encephalopathy.