# Review: Lactulose or lactitol may improve hepatic encephalopathy but may be less effective than antibiotics

Als-Nielsen B, Gluud LL, Gluud C. **Nonabsorbable disaccharides for hepatic encephalopathy.** Cochrane Database Syst Rev. 2004;(2):CD003044.

## QUESTION

In patients with hepatic encephalopathy (HE), what are the effects of nonabsorbable disaccharides (lactulose or lactitol)?

## METHODS

**Data sources:** Cochrane Hepato-Biliary Group Controlled Trials Register (March 2003), Cochrane Central Register of Controlled Trials (Issue 1, 2003), MEDLINE (1966 to March 2003), EMBASE/Excerpta Medica (1980 to March 2003), bibliographies of relevant studies; and contacting experts and pharmaceutical companies.

**Study selection and assessment:** Studies in any language were selected if they were randomized controlled trials (RCTs) comparing lactulose or lactitol with no intervention, placebo, or antibiotics; or comparing lactulose with lactitol in patients with HE and acute or chronic liver disease or fulminant hepatic failure. Studies were assessed for methodological quality, including method of randomization, allocation concealment, blinding, follow-up, and intention-to-treat analysis.

**Outcomes:** "No improvement" of HE (with improvement defined as partial or complete resolution of clinical or subclinical symptoms of HE) and all-cause mortality.

## MAIN RESULTS

30 RCTs met the inclusion criteria. 10 RCTs (280 patients, 75% men, median age 53 y) compared lactulose or lactitol with placebo or no intervention. 12 RCTs (698 patients, 72% men, median age 57 y) compared lactulose or lactitol with antibiotics. 8 RCTs (237 patients, 66% men, median age 56 y) compared lactulose with lactitol. Lactulose or lactitol was associated with a reduced risk for "no improvement" compared with placebo or no intervention but an increased risk for "no improvement" compared with antibiotics (Table). However, 2 trials of high methodological quality found no effect of nonabsorbable disaccharides on the risk for "no improvement" (RR 0.92, 95% CI 0.42 to 2.04). Lactulose or lactitol did not differ from placebo, no intervention, or antibiotics for rates of all-cause mortality. Lactulose and lactitol did not differ for risk for "no improvement" or all-cause mortality, but data were insufficient to draw firm conclusions.

## CONCLUSIONS

In patients with hepatic encephalopathy (HE), insufficient data exist on the effects of nonabsorbable dissacharides (lactulose or lactitol). Lactulose or lactitol may improve HE but may be less effective than antibiotics.

*Sources of funding: Denmark Pharmacy Foundation and Danish Center for Evaluation and Health Technology Assessment (DACEHTA).*

*For correspondence: Dr. B. Als-Nielsen, Copenhagen University Hospital, Copenhagen, Denmark. E-mail Bodil.a@ctu.rh.dk.*

**Lactulose or lactitol vs placebo, no intervention, or antibiotics for no improvement of hepatic encephalopathy at median 15 days***

| Number of studies (number of patients) | Comparisons | Weighted event rates | | RRR (95% CI) | NNT (CI) |
|---|---|---|---|---|---|
| 6 (207) | Lactulose or lactitol vs placebo or no intervention | 41% | 69% | 40% (23 to 53) | 4 (3 to 7) |
| | | | | RRI (CI) | NNH (CI) |
| 10 (600) | Lactulose or lactitol vs antibiotics | 37% | 29% | 27 (4 to 55) | 13 (7 to 100) |

*Abbreviations defined in Glossary; weighted event rates, RRR, RRI, NNT, NNH, and CI calculated from data in article using a fixed-effects model.

## COMMENTARY

HE is a neuropsychiatric syndrome caused by substantial dysfunction in acute or chronic liver disease. In acute liver failure, cerebral edema is the predominant cause of HE, with rapid progression to herniation if liver failure is irreversible. In advanced cirrhosis, HE is caused predominantly by the toxic effect of brain ammonia and by portosystemic shunting. HE can be spontaneous or precipitated by gastrointestinal bleeding, infection, or electrolyte disturbances; or be mimicked by drugs and alcohol. The presentation ranges from sudden alteration of consciousness to subtle personality changes; improvement with or without treatment is equally variable (1). The variability in the cause, presentation, and response to therapy in HE is an important limitation to interpreting results of treatment trials.

The systematic review by Als-Nielsen and colleagues is an excellent, comprehensive, critical assessment that questions the current dogma of using nonabsorbable disaccharides in HE. In this analysis of studies from their extensive search, comparisons of nonabsorbable disaccharides with placebo, antibiotics, or lactose (in lactase-deficient populations) showed no benefit of nonabsorbable disaccharides—particularly in the high-quality studies—but, interestingly, favored antibiotic therapy. The analysis is impeccable, using several accepted statistical instruments to address the heterogeneity of the trial methods and populations in the studies.

The salutary effect of catharsis or antibiotic therapy in HE treatment is due to the reduction in blood ammonia levels caused by decreases in colonic bacterial populations. Lactulose also reduces colonic luminal pH and apparently increases bacterial utilization of ammonia (2). Toxicity and bacterial resistance are problems with long-term antibiotic therapy. This review shows how flawed studies of a logical hypothesis can lead to widespread use of a treatment. Although these results show that nonabsorbable disaccharides are merely expensive cathartics, it is unlikely that practice patterns will change quickly. But we now have the basis to use a cheaper laxative that is not so sweet.

*Jacob Korula, MD, FRCPC*
*St. Vincent Medical Center*
*Los Angeles, California, USA*

***References***

1. **Conn HO, Bircher J.** Hepatic encephalopathy: syndromes and therapies. Bloomington, IL: Medi-Ed Press; 1994.
2. **Mortensen PB.** The effect of oral-administered lactulose on colonic nitrogen metabolism and excretion. Hepatology. 1992;16:1350-6.