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Non-Absorbable Disaccharides for Hepatic Encephalopathy: A Systematic Review and Meta-Analysis

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List of abbreviations

Non-absorbable disaccharides (NADs)

Hepatic encephalopathy (HE)

Randomized controlled trials (RCTs)

Electroencephalography (EEG)

Number Connection Test-A (NCT-A)

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Non-absorbable disaccharides (NADs) have been used to treat hepatic encephalopathy (HE) since 1966. However, a Cochrane review, published in 2004, found insufficient evidence to recommend their use in this context. This updated systematic review evaluates the effects of the NADs, lactulose and lactitol, for the treatment and prevention of HE in patients with cirrhosis. Thirty-eight randomized controlled trials (RCTs), involving 1828 patients, were identified *via* electronic and manual searches; 31 RCTs looked at the treatment of HE while seven looked at its primary/secondary prevention. Random-effects meta-analyses showed that, compared to placebo/no intervention, NADs had a beneficial effect on HE (relative risk [RR], 0.63; 95% confidence interval [CI], 0.53-0.74; Number Needed to Treat [NNT] = 4) and serious liver-related adverse events such as: liver failure, variceal bleeding, serious infections, spontaneous bacterial peritonitis and hepatorenal syndrome (RR, 0.42; 95% CI, 0.26-0.69; NNT = 50). Treatment was also associated with a reduction in mortality in patients with overt HE (RR, 0.36; 95% CI, 0.14-0.94; NNT = 20), although not in patients with minimal HE. Meta-analyses of the prevention RCTs showed that NADs prevented the development of HE (RR, 0.47; 95% CI, 0.33-0.68; NNT = 6), the risk of developing serious liver-related adverse events (RR, 0.48; 95% CI, 0.33-0.70; NNT = 6), and reduced mortality (RR, 0.63; 95% CI, 0.40-0.98; NNT = 20). Use of NADs was associated with non-serious gastrointestinal adverse events. There were no differences in the efficacy or safety of lactulose and lactitol. *Conclusions:* NADs have beneficial effects in the treatment and prevention of HE; their use, in this context, confers additional benefits including a reduction in serious liver-related morbidities and all-cause mortality.

In 1966, Johannes Bircher published the first report of the use of lactulose to treat hepatic encephalopathy (HE).[1, 2] This non-absorbable disaccharide (NAD) was adopted as the treatment of choice for this condition replacing dietary manipulation and the non-absorbable antibiotic neomycin. The second generation NAD, lactitol, was introduced into clinical practice in the 1980's.[3-6]

The NADs are classified as *osmotic laxatives*, but have also been classified as *prebiotics,* a generic term referring to agents that induce the growth or activity of commensal micro-organisms. Although the pathogenesis of HE is incompletely understood there is a general agreement that the gut-derived neurotoxin ammonia plays a key role.[7] NADs reduce the intestinal production/absorption of ammonia *via* several potential mechanisms, *viz*: (i) *catharsis*: the colonic metabolism of the NADs results in an increase in intraluminal gas formation and intraluminal osmolality and a reduction in intraluminal pH and transit time; (ii) *bacterial uptake of ammonia*: the volatile fatty acids released during the colonic metabolism of NADs are utilized as a preferred substrate by the colonic bacteria with ammonia as the nitrogen source for protein synthesis. The increase in bacterial numbers additionally 'bulks' the stool and contributes to the cathartic effect;[8] (iii) *intestinal ammonia production*: NADs inhibit glutaminase activity and interfere with the intestinal uptake of glutamine and its subsequent metabolism to ammonia;[9] (iv) *gut microbiome:* cirrhosis is associated with dysbiosis and changes in the colonic microbiome;[10] additional changes in the microbiome may be observed in patients with HE.[11] NADs can beneficially affect microbiota composition.[11]

The efficacy and safety of NADs for the treatment of HE has been assessed in a number of randomized controlled trials (RCTs) although many of the earlier studies can be

criticized, if judged by today's much more rigorous standards. A Cochrane review, published in 2004,[12] evaluated NADs versus placebo or no intervention and found a beneficial effect on HE, but no effect on mortality. However, there were a number of methodological issues including the reporting of bias domains and the lack of statistical power, which weakened the strength of the conclusions. The publication of this review did, however, resulted in the undertaking and publication of a large number of additional RCTs of relevance.

In 2014, the European and American Associations for the Study of the Liver (EASL/AASLD) published a joint practice guideline in which they recommended lactulose as the treatment of choice for overt HE and for its secondary prevention after an index event.[13] They did not recommend routine treatment for minimal HE, but stated that exceptions could be made, on a case-by-case basis, if driving skills, work performance, quality of life or cognitive function were impaired. They did not recommend primary prophylaxis for the prevention of HE except in patients 'known to be at high risk' but not otherwise defined. The guideline mentioned that lactitol is preferred in some centers but did not comment on the relative efficacy and safety of the two agents. The authors of the EASL/AASLD practice guideline based their recommendations on clinical experience and on a formal review and analysis of recently published literature.

The advent of the new RCTs and the contrary views expressed in the 2004 Cochrane review and the 2014 EASL/AASLD practice guideline prompted this update of the use of NADs in patients with cirrhosis. The updated review includes a larger number of RCTs and is based on the current methodology for systematic reviews. Unlike the 2004

Cochrane review, the primary outcomes now include serious adverse events as well as hepatic encephalopathy and mortality.

Materials and Methods

This paper is an abbreviated version of an updated and revised Cochrane systematic review.[12] It addresses the clinical utility and safety of NADs for the treatment and prevention of hepatic encephalopathy in patients with cirrhosis in comparison with placebo/no intervention.

Data Sources and Searches. A language-unrestricted search was made of the Cochrane Hepato-Biliary Group Controlled Trials Register, the Cochrane Library, MEDLINE, EMBASE, and Science Citation Index. The generic search strategy was devised by the Trial Search Coordinator at the Cochrane Hepato-Biliary Editorial Team; it was then adjusted for each different search platform (Supplementary Table 1). The last search update was undertaken in December 2015.

In addition, the bibliographies of relevant papers, specialist journals, conference proceedings, and trial registries were searched and contact made with the principal authors of published trials, and relevant pharmaceutical companies to obtain missing or additional trial data.

Study Selection. Two review authors (LG and MYM) independently scrutinized the electronic searches, performed the additional manual searches, and listed all potentially eligible RCTs. All three authors reviewed this material and participated in the final selection of RCTs, which was agreed by consensus. RCTs were included regardless of their publication status, language, blinding, or design. Only the first period of cross-over trials, in which patients were randomized to lactulose/lactitol or placebo/no intervention, was included.[14]

Translations of non-English papers were obtained from commercial translation services or medical personnel fluent in the relevant language.

Data Extraction. Two review authors independently retrieved preselected data from the selected RCT reports including:

i) *Study-specific information*: date of publication; inclusion period; investigation sites; study design;

ii) *Patient-specific information*: age, gender distribution, aetiology of cirrhosis, type of hepatic encephalopathy; previous history of hepatic encephalopathy;

iii) *Treatment –specific information*: comparative regimens; numbers of patients assigned to each intervention arm; dose, duration and pattern of treatment; mode of administration; use of adjuvant anti-encephalopathy treatment;

iv) *Information on evaluation/outcome variables*, *viz:* mental state, which was usually assessed using the West Haven criteria;[15] asterixis; Number Connection Test-A (NCT-A) time;[16] other psychometric test results; venous/arterial blood ammonia concentrations; electroencephalogram (EEG) mean dominant frequency (mdf). These variables were used in combination, in several studies, often after transformation using a semi-quantitative scoring system, to provide a composite 'overall assessment of hepatic encephalopathy'. The scoring schema most frequently used was the Portal-Systemic Encephalopathy (PSE) sum/index,[15] which is calculated utilizing five variables, *viz:* mental status, the presence and severity of asterixis; the NCT-A time, blood ammonia concentration; and the EEG mdf. Each variable is assigned a score of 0 (no abnormality) to 4 (severe abnormality) and the PSE index calculated as the

ratio of the points scored and the maximum possible score of 28. The assessment of HE outcome was based on the authors' evaluation.[17] Data on quality of life were extracted where available.

Independent data collections were compared and contrary opinions resolved through discussion.

Outcome Measures. All outcomes were evaluated at the maximum duration of follow up.[18] The *primary* outcome measures were hepatic encephalopathy *viz.* the number of patients without clinically relevant improvement; all-cause mortality, and serious adverse events, which in this population were inevitable related to the underlying liver disease, for example: liver failure, variceal hemorrhage, serious infections, including spontaneous bacterial peritonitis, and hepatorenal syndrome. The *secondary* outcomes measures were quality of life and non-serious adverse events such as abdominal pain, diarrhea, vomiting, nausea, flatulence, anorexia and headache.

Assessment of Bias Risk. The assessment of bias control was based on six domains *viz:* selection bias, performance and detection bias, attrition bias, reporting bias, for-profit bias and other bias, (Supplementary Table 2).[18] The risk of bias for the individual domains was classified as low, unclear (insufficient information provided), and high. The six domains were combined into an overall score which was classified as *low* if all six individual domains were classified as low risk of bias and *high* if one or more of the domains was classified as unclear/high risk of bias.

Data synthesis and analysis. Outcomes were analyzed using random-effects meta-analyses[18] and the effect measures reported as relative risk (RR) or mean differences

(MD) with 95% confidence intervals (CIs) and I^2 values as a marker of heterogeneity. I^2 values of zero to 40% were classified as unimportant; 40 to 60% as moderate; 60 to 80% as substantial, and >80% as considerable. For statistically significant primary outcomes, the numbers needed to treat (NNT) was calculated using 1/risk difference based on the best available evidence defined as RCTs with a low risk of bias in the overall assessment if available. For meta-analyses which included at least ten trials, publication bias and other small study effects were assessed using regression analyses.[19]

Separate analyses were undertaken of RCTs evaluating the treatment of HE and the prevention of HE. In addition, subgroup and sensitivity analyses were undertaken to analyse RCTs (i) with a low risk of bias; and those evaluating: (ii) minimal or overt HE; (iii) acute (episodic) or chronic (recurrent and persistent) HE and (iv) primary or secondary prevention;

The analyses were performed using RevMan version 5 (Nordic Cochrane Centre, Copenhagen Denmark) and STATA version 14 (Stata Corp, Texas USA). The results are reported based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.[20]

Results

Search results. The electronic searches generated 1378 potentially eligible records while the manual searches identified an additional 10 records (Fig. 1). After removal of duplicate and irrelevant references, a total of 82 records remained and were retrieved for further assessment. Of these, 38 RCTs[4-6, 21-55] fulfilled the inclusion criteria (Table 1). Qualitative data were available from all 38 trials, involving 1828 patients, while quantitative data were available from 34 trials, involving 1764 patients.

Included RCTs. The utility of NADs for the *treatment* of HE was evaluated in 31 RCTs. Sixteen of these RCTs evaluated treatment effects in patients with overt HE classified as either acute (seven RCTs) or chronic (nine RCTs). In the latest recommended nomenclature,[13] the diagnosis 'acute' HE corresponds to the term 'episodic' while 'chronic' HE corresponds to the terms recurrent or persistent (Supplementary Table 3). The remaining 15 RCTs evaluated treatment effects in patients with minimal HE.

The *prevention* of HE was evaluated in seven RCTs. Three RCTs evaluated primary prevention in patients with no previous history of HE or secondary prevention in people with no immediately obvious risk factors for HE. The remaining four RCTs included patients with an increased risk of HE due to gastrointestinal bleeding, recent insertion of a transjugular intrahepatic portosystemic shunt, or portosystemic shunt surgery. Six of the prevention trials compared NADs versus placebo/no intervention while the remaining prevention trial compared lactulose versus lactitol.

In total, 29 trials compared NADs versus placebo/no intervention (Table 1) and nine compared lactulose versus lactitol. The duration of follow-up in the individual RCTs

varied in relation to the type of HE and the study design. Thus, the duration of follow-up was four to seven days in RCTs evaluating acute HE, 10 to 360 days in RCTs evaluating chronic HE; 14 to 180 days in RCTs evaluating minimal HE and 5 to 360 days in RCTs evaluating prevention depending on whether this was primary or secondary.

A variety of methods were used, in the included RCTs to assess patients' neuropsychiatric status and to classify outcomes (Supplementary Table 3). Eight used the PSE Sum/Index.[5, 6, 29, 36, 40, 41, 48, 49] Two used the PSE Sum/Index modified by omission of the EEG[27] and replacement of the NCT-A with the Digit Symbol test.[39] Ten of the remaining RCTs used West Haven Criteria to assess mental status.[21, 31, 32, 35, 37, 43-45, 51, 55] Three RCTs used the Conn Score, which is similar to the West Haven Criteria.[4, 28, 50] Thirty-two RCTs employed NCT-A.[4-6, 21, 24, 26-41, 43, 45, 46, 48-55] Twenty-five RCTs measured blood ammonia in plasma, venous, or arterial blood.[5, 6, 21-23, 25-29, 31, 35, 36, 38-41, 44, 46-49, 52, 54, 55] while 22 assessed the electroencephalogram mean cycle frequency.[4-6, 21-23, 25, 26, 28-30, 32, 36, 38-42, 48, 49, 52, 54]

Bias Assessment. The risk of *selection* bias was low in 23 RCTs (Supplementary Table 4). Fourteen RCTs were conducted double blind and so had a low risk of *performance* and *detection* bias while six were conducted with a blinded outcome assessment and had a low risk of *detection* bias. The risk of *attrition* bias was low in 22 RCTs while the risk of *outcome* bias was low in 32 trials. Nineteen trials were free of *for-profit funding* bias. No other biases were identified. In the overall bias assessment, eight RCTs were classed as of low risk of bias in the analysis of mortality. None was classified as of low risk in the assessment of the remaining outcomes.

TREATMENT TRIALS COMPARING NADS VERSUS PLACEBO/NO INTERVENTION

Primary outcomes. Treatment with NADs was associated with a beneficial effect on HE compared to placebo/no intervention (RR, 0.63; 95% CI: 0.53-0.74; NNT = 4; 747 patients; 16 RCTs; I^2 = 25%) (Fig. 2). This effect was seen in the five RCTs evaluating overt HE (RR, 0.62; 95% CI: 0.39-0.99; 140 patients; NNT = 5) and in the 11 RCTs evaluating minimal HE (RR, 0.63; 95% CI: 0.52-0.76; 607 patients; NNT = 4). Within the overt HE group treatment was equally effective in those with acute and chronic HE (data not shown).

Treatment with NADs had a beneficial effect on mortality (RR, 0.49; 95% CI: 0.23-1.05; NNT = 100; 819 patients; 18 RCTs; I^2 = 0%) (Fig. 3). This effect was seen in the six RCTs evaluating overt HE (RR, 0.36; 95% CI: 0.14-0.94; 172 patients; NNT = 20), but not in the 12 RCTs evaluating minimal HE (RR, 0.82; 95% CI: 0.24-2.86; 647 patients). Within the overt HE group, treatment had a beneficial effect on mortality in patients with acute HE. The results in the chronic HE group were not separately estimable (data not shown). Three of the included RCTs had a low risk of bias. All three included patients with minimal HE. Analysis of the three trials found no effect of NADs on mortality (RR 0.56, 95% CI 0.12 to 2.86).

The serious adverse events reported were primarily liver-related and included liver failure, variceal bleeding, severe infections, primarily respiratory and urinary tract, spontaneous bacterial peritonitis, and hepatorenal syndrome. Treatment with NADs was associated with a beneficial effect on serious adverse events (RR, 0.42; 95% CI: 0.26-0.69; NNT = 50; I^2 = 0%; 819 patients; 18 RCTs). The effect was seen both in patients with overt HE (RR, 0.40; 95% CI, 0.16-0.1.02; NNT = 25; 140 patients; six RCTs) and in patients with

minimal HE (RR, 0.43; 95% CI, 0.24-0.78; NNT = 50; 607 patients; 12 RCTs). Within the overt HE group, treatment reduced the risk of serious adverse events in patients with acute HE, but the result in the chronic HE group was not separately estimable (data not shown). There were no differences in serious adverse events between the intervention and control groups when they were analyzed individually rather than collectively (Supplemental table 5).

None of the analyses of the primary outcomes showed evidence of publication bias or other small study effects in regression analyses.

Secondary outcomes. Six RCTs included quality of life data; three RCTs involving 160 patients with minimal HE utilized the *Sickness Impact Profile* allowing the results to be analyzed. Two of these RCTs found a beneficial effect of lactulose reflected in the change in the overall score from baseline to the end of treatment (MD, 7.18; 95% CI, 5.28-9.07; I^2 = 53%), while the third trial found no difference between end of treatment values (MD 0.90; CI -4.13-5.93).

Treatment with NADs was associated with an increased risk of non-serious adverse events, including diarrhea, bloating, flatulence and nausea. However, the risk of these events did not differ between patients allocated to NADs or placebo/no intervention (RR, 2.12; 95% CI, 0.62-7.28; 201 patients, five RCTs, I^2 = 62%).

NAD VERSUS PLACEBO/NO INTERVENTION: PREVENTION RCTS

Primary outcomes. NADs had a beneficial effect on the prevention of HE when all six trials were included (RR, 0.47; 95% CI, 0.33-0.68; NNT = 6; 668 patients, I^2 = 30%) and when including the five RCTs with a low risk of bias (RR, 0.50; 95% CI, 0.35-0.71, NNT =

5; 538 patients; I^2 = 27%). NADs had utility for both the primary (RR, 0.48; 95% CI: 0.23-0.98; NNT = 7; 370 patients; four RCTs) and secondary prevention of HE (RR, 0.44; 95% CI: 0.31-0.64; NNT = 4; 298 patients; two RCTs).

NADs had a beneficial effect on mortality compared to placebo/no intervention when all six RCTs were included (RR, 0.47; 95% CI: 0.33-0.68; NNT = 20; 668 patients; I^2 = 0%) or when including the five RCTs with a low bias risk (RR 0.64, 95% CI 0.41 to 0.99; NNT = 33) (Fig. 4). However, the effect was not seen in subgroup analyses of the four primary prevention RCTs (RR, 0.56; 95% CI, 0.27-1.17) or the two secondary prevention RCTs (RR, 0.67; 95% CI, 0.39-1.16).

Treatment with NADs reduced the risk of developing serious adverse events in the analysis of the six prevention RCTs (RR 0.63, 95% CI 0.40 to 0.98; NNT = 6; I^2 = 0%) and when analyzing primary (RR, 0.50; 95% CI: 0.24-1.03; NNT = 8) or secondary prevention (RR, 0.44; 95% CI: 0.31-0.64; NNT = 4). There were no differences in serious adverse events between the intervention and control groups when the events were analyzed individually rather than collectively (Supplemental table 5).

Secondary outcomes. None of the prevention RCTs reported data on quality of life. Use of NADs in prevention trials increased the risk of non-serious adverse events such as bloating, diarrhea, and nausea (RR, 2.78; 95% CI, 1.50-5.13; 548 patients; four RCTs).

LACTULOSE VERSUS LACTITOL: TREATMENT AND PREVENTION.

There were no difference between the effects of lactulose versus lactitol on HE (RR, 1.00; 95% CI: 0.84-1.19; 194 patients; seven RCTs), serious adverse events (RR, 1.56; 95%

CI, 0.84-2.88; 245 patients; nine RCTs), mortality (RR, 1.30; 95% CI: 0.59-2.85; 225 patients; eight RCTs), or in the occurrence of non-serious gastrointestinal adverse events (RR, 1.55; 95% CI, 0.88-2.74; 169 patients; six RCTs).

Discussion

This updated Cochrane review, found evidence that NADs have effects which are beneficial in the management of patients with minimal and overt HE, but also for the primary and secondary prevention of HE. The use of NADs, in these situations, is also associated with a reduction in the risk of developing serious liver-related complications such as liver failure, variceal hemorrhage, severe infections, spontaneous bacterial peritonitis and hepatorenal syndrome. In addition, where NADs are used to treat overt HE or for HE prevention, there is an associated reduction in mortality. As expected, use of NADs increases the occurrence of non-serious gastrointestinal side-effects such as bloating and nausea. No discernable differences were observed in the efficacy and safety of the two available NADs, lactulose and lactitol.

The reduction in the risk of developing serious liver-related complications and the reduction in all-cause mortality associated with use of NADs may relate to an effect on the gut microbiome.[11, 56] The presence of chronic liver disease is associated with gut dysbiosis which has a number of important clinical consequences, including the promotion of pathological bacterial translocation,[57] which plays an important role in the development of infection, and may also trigger development of a profound inflammatory state and exacerbate hemodynamic derangements.[58] These changes are felt to be key to the development of many of the clinical complications of cirrhosis. The beneficial effects of NADs on the gut microbiome may interfere with this sequence of events.

Overall Completeness and Applicability of the Evidence. Information was provided, in this review, on the major outcomes of concern in the population under study, namely:

morbidity, mortality, adverse events and quality of life. HE varies widely in its manifestation and the RCTs included in this systematic review, represent the entire spectrum of the syndrome encountered in people with cirrhosis.

Episodes of HE often develop in response to a precipitating event such as infection or gastrointestinal bleeding. Identification and treatment of these precipitating factors is key to the management of affected individuals, although no obvious precipitating factor is identified in 50% of instances. The RCTs included in this review did not provide detailed information on possible precipitating factors, nor on the effects of interventions designed to ameliorate them. Thus, it is not possible to discern whether use of NADs provides additional benefit in these situations. However, in two of the included RCTs, NADs, used together with measures to manage upper gastrointestinal hemorrhage, effectively prevented the development of HE.

Patients with HE impose a significant burden on health care systems, and the resource utilization associated with their management, in particular the need for hospitalization and aftercare, is increasing.[59, 60] None of the trials in the present review looked directly at the cost-benefits of treatment but it is likely that effective treatment would shorten hospitalization while effective prophylaxis would obviate the need for admission. In this regard NADs are cheap and likely to be highly cost-effective.

Agreements with Other Reviews and Guidelines. The previous version of this review, published in 2004,[12] included 10 RCTs comparing NADs versus placebo/no intervention; six evaluated the treatment of overt HE and four the treatment of minimal HE. The review found that NADs had a beneficial effect on HE compared with placebo/no intervention,

but that they had no effect on mortality. The review did not assess serious adverse events. Based on the high risk of bias and the small number of RCTs, the authors concluded that there was insufficient evidence to determine whether NADs have a significant beneficial effect on patients with HE.

The results of this updated review, in contrast, provide consistent evidence that use of NADs is associated with beneficial effects on HE, serious liver-related adverse events and mortality. This review was undertaken based on current methodological recommendations and employed more extensive manual searches in order to identify RCTs, which may be missed in the electronic searches. In total 38 RCTs comparing NADs versus placebo/no intervention were included; of these 16 evaluated the treatment of overt HE; 15 the treatment of minimal HE and seven the prevention of HE. Serious adverse events were included as a primary outcome measure.

The recommendations of the joint EASL/AASLD Practice Guidelines on HE in chronic liver disease[13] are relevant to the present review. Thus, the guideline recommends that lactulose should be the first-choice treatment for an episode of overt HE in patients with cirrhosis and for the prevention of recurrent episodes of HE after an index event. The findings of this systematic review would support these recommendations. The guideline does not recommend routine treatment for minimal HE or primary prophylaxis for prevention of the development of HE except in patients known to be at high risk. This review supports a more proactive, evidence-based approach. Thus, it provides a large body of evidence to show that patients with minimal HE benefit from NADs in relation to cognitive functioning and probably also quality of life. It also provides evidence supporting the use of NADs for primary prophylaxis in patients with cirrhosis to prevent

the development of HE. These results and their financial implications should be considered in the formulation of future versions of the EASL/AASLD guideline.

Conclusion. This updated 2016 systematic Cochrane review on the efficacy and safety of NADs for the treatment and prevention of HE, in patients with cirrhosis found sufficient evidence to reach conclusions and make recommendations for clinical practice. Use of NADs had a significant beneficial treatment effect on HE, both minimal and overt, and an overall beneficial effect on both liver-related morbidity and all-cause mortality. In addition use of NADs provides effective prophylaxis against the development of HE in both the primary and secondary setting. Notwithstanding the differences in the robustness of the sub-group analyses these effects are consistent and support the use of NADs as a first line treatment for HE in patients with cirrhosis and for its prevention.

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Contributors: LL Gluud drafted the revised review, identified and selected trials, contributed to the data extraction analyses and interpretation of the results, and revised the review. H Vilstrup identified and selected trials, contributed to the data extraction analyses and interpretation of the results, and revised the review. MY Morgan identified and selected trials, contributed to the data extraction analyses and interpretation of the results, and revised the review.

Ethical approval: not applicable

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and have made the following declarations: LLG is a co-author of previous reviews of the treatment of hepatic encephalopathy; MYM and HV were primary investigators of randomized controlled trials evaluating the treatment of hepatic encephalopathy; HV was the Chairman of the joint EASL and AASLD practice guideline development group on hepatic encephalopathy and first author of the published guideline. LLG has participated in scientific meetings in Denmark, Sweden, and Finland sponsored by Norgine who market rifaximin, an alternative treatment for hepatic encephalopathy and has participated in clinical trials on inflammatory bowel disease and

clostridium difficile enteritis sponsored by Abbvie and Merck. None of the authors has had a financial relationship with organizations that might have an interest in the submitted work in the previous three years and no other relationships or activities that might have influenced the submitted work.

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Legends to Figures

Fig. 1. Trial flow chart.

Fig. 2. Random-effects meta-analysis of randomized controlled trials comparing the efficacy of non-absorbable disaccharides versus placebo/no intervention on hepatic encephalopathy in patients with cirrhosis, both overall and by type of encephalopathy

Fig. 3. Random-effects meta-analysis of randomized controlled trials comparing the effect of non-absorbable disaccharides versus placebo/no intervention on mortality in patients with cirrhosis with either overt or minimal hepatic encephalopathy.

Fig. 4. Random-effects meta-analysis of prevention randomized controlled trials comparing the effects of non-absorbable disaccharides versus placebo/no on mortality in patients with cirrhosis, both overall and by type of prevention.

Table 1. Characteristics of the randomized controlled trials included in the systematic review of non-absorbable disaccharides for the treatment and prevention of hepatic encephalopathy in patients with cirrhosis

Agrawal 2012[21]	
Methods	Open, parallel-arm, single-center trial.
Category	Secondary prophylaxis.
Patients	158 patients with cirrhosis and previous overt HE. The trial evaluates secondary prevention of HE.
Interventions	Lactulose syrup versus no intervention for 12 months.
Inclusion period	October 2008 to December 2009.
Country	India.
Brown 1971[22]	
Methods	Double-blind, cross-over, single-center trial.
Category	Treatment: overt, chronic.
Patients	20 patients with advanced cirrhosis stabilized in hospital on a low protein diet and then given increasing amounts of protein until they developed overt HE.
Interventions	Lactulose syrup versus placebo (sorbitol) for a maximum of 30 months.
Inclusion period	Not reported.
Country of origin	USA.
Corazza 1982[23]	
Methods	Double-blind, parallel-arm, single-center trial.
Category	Treatment: overt, chronic.
Patients	32 patients with cirrhosis and chronic HE.
Interventions	Lactulose syrup versus placebo for 10 days.

Inclusion period	Not reported.
Country of origin	Italy.
Dhiman 2000[24]	
Methods	Open, parallel-arm, single-center trial.
Category	Treatment: minimal.
Patients	26 patients with cirrhosis and minimal HE.
Interventions	Lactulose syrup versus no intervention for 3 months.
Inclusion period	Not reported.
Country of origin	India.
Elkington 1969[25]	
Methods	Double-blind, cross-over, single-center trial.
Category	Treatment: overt, chronic.
Patients	7 patients with decompensated cirrhosis and chronic overt HE.
Interventions	Lactulose syrup versus placebo (sorbitol) for 15 days.
Inclusion period	Not reported.
Country of origin	USA.
Germain 1973[26]	
Methods	Double-blind, parallel-arm, single-center trial.
Category	Treatment: overt, chronic.
Patients	18 patients with cirrhosis who developed chronic overt HE after portal-systemic shunt surgery.
Interventions	Lactulose syrup versus placebo (saccharose–based) for 15 days
Inclusion period	Not reported.
Country of origin	France.

Grandi 1991[27]	
Methods	Open, cross-over, single-center trial.
Category	Treatment: overt, chronic.
Patients	40 patients with cirrhosis and chronic overt HE.
Interventions	Crystalline lactulose versus lactitol for 60 days.
Inclusion period	Not reported.
Country of origin	Italy.
Heredia 1987[28]	
Methods	Open, parallel-arm, single-center trial
Category	Treatment: overt, acute.
Patients	40 patients with cirrhosis and an acute episode of overt HE. In total, 65% had a previous history of overt HE.
Interventions	Lactulose syrup versus lactitol for 5 days.
Inclusion period	Not reported.
Country of origin	Spain.
Heredia 1988[29]	
Methods	Open, cross-over, single-center trial.
Category	Treatment: overt, chronic.
Patients	20 patients with cirrhosis and previous portal-systemic shunt surgery with chronic/recurrent overt HE. The trial originally included 25 patients, but excluded two patients who died and three who dropped out.
Interventions	Lactulose syrup versus lactitol for 3 months.
Inclusion period	Not reported.
Country of origin	Spain.
Horsmans 1997[30]	

Methods	Double-blind, parallel-arm, single-center trial.
Category	Treatment: overt, minimal.
Patients	14 patients with cirrhosis and minimal HE.
Interventions	Crystalline lactulose versus placebo (lactose) for 15 days.
Inclusion period	Not reported.
Country of origin	Belgium.
Jain 2013[31]	
Methods	Open, parallel-arm, single-center trial.
Category	Treatment: overt, minimal.
Patients	60 patients with cirrhosis and minimal HE.
Interventions	Lactulose syrup versus no intervention for 3 months.
Inclusion period	October 2011 to February 2012.
Country of origin	India.
Jankovic 1996[32]	
Methods	Open, parallel-arm, single-center trial.
Category	Treatment: overt, acute.
Patients	16 patients with cirrhosis and an acute episode of overt HE.
Interventions	Lactulose syrup versus lactitol for 5 to 7 days.
Inclusion period	Not reported.
Country of origin	Serbia.
Li 1999[33]	
Methods	Open, parallel-arm, multicenter trial.
Category	Treatment: overt, minimal.
Patients	86 patients with cirrhosis and minimal HE.
Interventions	Lactulose syrup versus no intervention for 30 days.

Inclusion period	January 1997 to January 1998.
Country of origin	China.
McClain 1984[34]	
Methods	Double-blind, parallel-arm, single-center trial.
Category	Treatment: overt, minimal.
Patients	32 patients with cirrhosis and minimal HE.
Interventions	Lactulose syrup versus placebo (sucrose) for 3 months.
Inclusion period	Not reported.
Country of origin	USA.
Mittal 2011[35]	
Methods	Open, parallel-arm, single-center trial.
Category	Treatment: overt, minimal.
Patients	80 patients with cirrhosis and minimal HE.
Interventions	Lactulose syrup versus no intervention for 3 months.
Inclusion period	October 2007 to October 2009
Country of origin	India.
Morgan 1987[5]	
Methods	Double-blind, parallel-arm, single-center trial.
Category	Treatment: overt, acute.
Patients	25 patients with cirrhosis randomized during 28 acute episodes of overt HE. Only the first randomization period is included in the analyses.
Interventions	Lactulose versus lactitol as identically presented liquids for 5 days.
Inclusion period	July 1984 to December 1985.
Country of origin	United Kingdom.

Morgan 1987[6]	
Methods	Double-blind, cross-over, single-center trial.
Category	Treatment: overt, chronic.
Patients	12 patients with cirrhosis and chronic overt HE.
Interventions	Lactulose versus lactitol as identically presented liquids for 3 months.
Inclusion period	November 1985 to February 1986.
Country of origin	United Kingdom.
Morgan 1989[4]	
Methods	Single-blind, cross-over, single-center trial.
Category	Treatment: overt, minimal.
Patients	20 patients with cirrhosis, minimal HE, and no history of overt HE.
Interventions	Lactulose syrup versus lactitol for 2 months.
Inclusion period	October 1986 to April 1988.
Country of origin	United Kingdom.
Pai 1995[36]	
Methods	Single-blind, parallel-arm, single-center trial.
Category	Treatment: overt, acute.
Patients	41 patients with cirrhosis and an acute episode of overt HE.
Interventions	Lactulose syrup versus lactitol for 5 days.
Inclusion period	April 1993 to April 1994.
Country of origin	Taiwan.
Prasad 2007[37]	
Methods	Open, parallel arm, single-center trial.
Category	Treatment: overt, minimal.

Patients	61 patients with cirrhosis and minimal HE.
Interventions	Lactulose syrup versus no intervention for 3 months.
Inclusion period	January 2004 to March 2005.
Country of origin	India.
Quero 1997[38]	
Methods	Double-blind, parallel-arm, single-center trial.
Category	Treatment: overt, minimal.
Patients	40 patients with cirrhosis and minimal HE.
Interventions	Crystalline lactulose versus lactose placebo for 6 months.
Inclusion period	October 1992 to September 1994.
Country of origin	Holland.
Raza 2004[39]	
Methods	Open, parallel-arm, single-center trial.
Category	Treatment: overt, acute.
Patients	31 patients with cirrhosis and an acute episode of overt HE.
Interventions	Lactulose enemata versus tap water enemata administered for a mean of 4.5 days. Both groups also received oral lactulose.
Inclusion period	Not reported.
Country of origin	Pakistan.
Riggio 1989[40]	
Methods	Single-blind, parallel-arm, single-center trial.
Category	Prophylaxis: Primary/secondary.
Patients	31 patients with cirrhosis who had undergone portal-systemic shunt surgery. The trial evaluates primary prevention for 53.3% of patients in the lactulose group and 62.5% of patients in the lactitol group and secondary prevention for the remaining patients. The trial only provided data for the

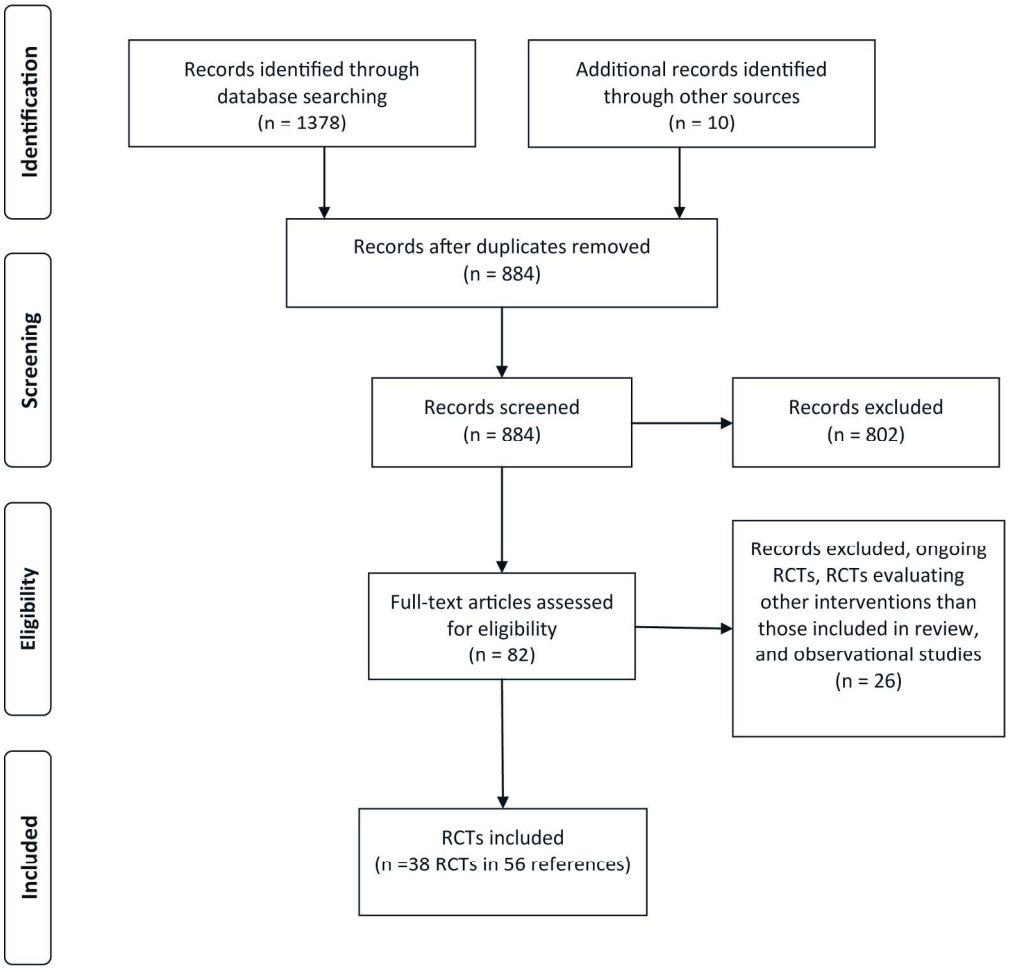
	analyses of mortality.
Interventions	Lactulose syrup versus lactitol for 6 months.
Inclusion period	Not described.
Country of origin	Italy.
Riggio 2005[41]	
Methods	Single-blind, parallel-arm, single-center trial.
Category	Prophylaxis: Primary.
Patients	50 patients with cirrhosis randomized immediately after transjugular intrahepatic portosystemic shunt placement. The trial evaluates primary prevention for 92% in the lactitol group and 76% in the control group and secondary prevention for remaining patients. We therefore included the trial as primary prevention in our subgroup analyses.
Interventions	Lactitol versus no intervention for 6 months.
Inclusion period	November 1998 to September 2003.
Country of origin	Italy.
Rodgers 1973[42]	
Methods	Double-blind, cross-over, single-center, outpatient trial.
Category	Treatment: overt, chronic.
Patients	6 patients with cirrhosis and chronic overt HE. Three are described in detail.
Interventions	Lactulose syrup versus placebo (sorbitol).
Inclusion period	1967 to 1970.
Country of origin	USA.
Sharma 2009[43]	
Methods	Open, parallel-arm, single-center, outpatient trial.
Category	Prophylaxis: Secondary.
Patients	140 patients with cirrhosis who had recovered from an

	episode of overt HE. The trial evaluates secondary prevention of HE.
Interventions	Lactulose syrup versus no intervention for 12 months.
Inclusion period	January 2006 to June 2008.
Country of origin	India.
Sharma 2011[44]	
Methods	Open, parallel-arm, single-center, inpatient trial.
Category	Prophylaxis: Primary.
Patients	70 patients with cirrhosis who were stable after an acute variceal bleed. The trial evaluates primary prevention of HE in 83% of patients in the lactulose group and 86% of patients in the control group and secondary prevention in the remaining patients. We included the trial as primary prevention in our subgroup analyses.
Interventions	Lactulose syrup versus no intervention for 120 hours.
Inclusion period	December 2008 to January 2010.
Country of origin	India.
Sharma 2012[45]	
Methods	Open, parallel-arm, single-center, outpatient trial.
Category	Prophylaxis: Primary.
Patients	120 patients with cirrhosis and no history of overt HE. The trial evaluates primary prevention of HE.
Interventions	Lactulose syrup versus no intervention for 12 months.
Inclusion period	January 2008 to September 2009.
Country of origin	India.
Shi 1997[46]	
Methods	Double-blind, parallel-arm, single-center, outpatient trial.
Category	Treatment: overt, minimal.

Patients	31 patients with cirrhosis and minimal HE.
Interventions	Lactitol versus placebo (glucose) for 2 weeks.
Inclusion period	Not reported.
Country of origin	China.
Simmons 1970[47]	
Methods	Double-blind, parallel-arm, single-center trial.
Category	Treatment: overt, acute.
Patients	26 patients with cirrhosis; 22 patients with acute HE and 4 with classified as chronic remittent HE. The trial was included in the subgroup analysis of acute HE.
Interventions	Lactulose syrup versus placebo (glucose) for 10 days.
Inclusion period	Not reported.
Country of origin	USA.
Uribe 1987[48]	
Methods	Double-blind, cross-over, single-center trial.
Category	Treatment: overt, acute.
Patients	37 patients with cirrhosis included during 45 acute episodes of overt HE. Data could not be extracted from the first randomization period.
Interventions	Rectal lactitol enemata versus rectal placebo enemata (lactose or tap water) for 4 days.
Inclusion period	Not reported.
Country of origin	Mexico.
Uribe 1987[49]	
Methods	Double-blind, cross-over, single-center trial.
Category	Treatment: overt, chronic.
Patients	20 patients with cirrhosis and chronic overt HE.

Interventions	Lactitol versus placebo (lactose) for 2 weeks.
Inclusion period	Not reported.
Country of origin	Mexico.
Watanabe 1997[50]	
Methods	Open, parallel-arm, multicenter trial.
Category	Treatment: overt, minimal.
Patients	75 patients with cirrhosis, minimal HE and previous overt HE.
Interventions	Lactulose syrup versus no intervention for 8 weeks.
Inclusion period	Not reported.
Country of origin	Japan.
Wen 2013[51]	
Methods	Open, parallel-arm, single-center trial.
Category	Prophylaxis: Primary.
Patients	130 patients with cirrhosis experiencing an acute upper gastrointestinal hemorrhage and no evidence of overt or minimal HE at inclusion. The trial evaluates primary prevention of HE.
Interventions	Lactulose syrup versus no intervention for 7 days.
Inclusion period	May 2007 to July 2011.
Country of origin	China.
Xing 2003[52]	
Methods	Open, parallel-arm, single-center trial.
Category	Treatment: overt, minimal.
Patients	45 patients with cirrhosis and minimal HE.
Interventions	Lactulose syrup versus no intervention for 4 weeks.
Inclusion period	February 2000 to March 2002.

Country of origin	China.
Yao 2014[53]	
Methods	Open, parallel-arm, single-center trial.
Category	Treatment: overt, minimal.
Patients	40 patients with cirrhosis and minimal HE.
Interventions	Lactulose syrup versus no intervention for 15 days.
Inclusion period	May 2011 to July 2013.
Country of origin	China.
Zeng 2003[54]	
Methods	Open, parallel-arm, single-center trial.
Category	Treatment: overt, minimal.
Patients	60 patients with cirrhosis and minimal HE.
Interventions	Lactulose syrup versus no intervention for eight or 24 weeks.
Inclusion period	July 1998 to March 2002.
Country of origin	China.
Ziada 2013[55]	
Methods	Single-blind, parallel-arm, single-center trial.
Category	Treatment: overt, minimal.
Patients	60 patients with cirrhosis and minimal HE.
Interventions	Lactulose syrup versus no intervention for 4 weeks.
Inclusion period	March 2010 to January 2012.
Country of origin	Egypt.



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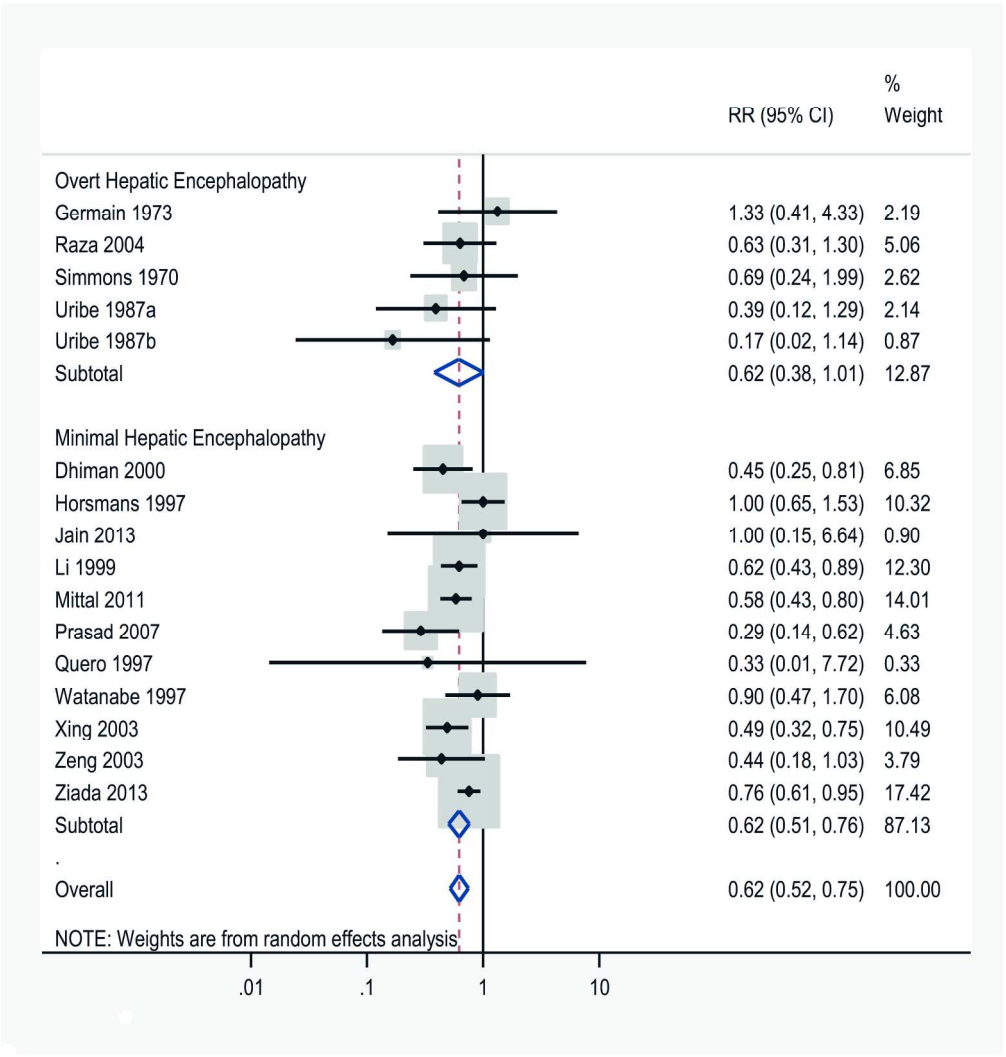

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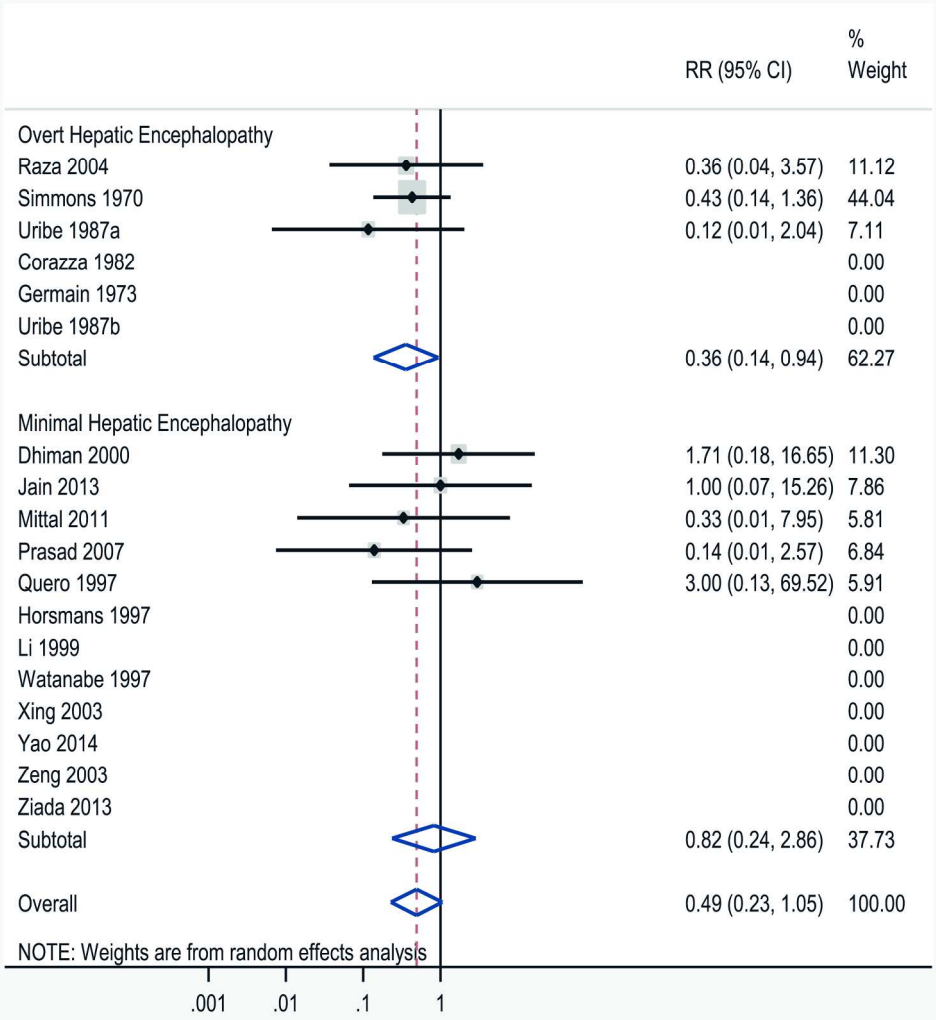

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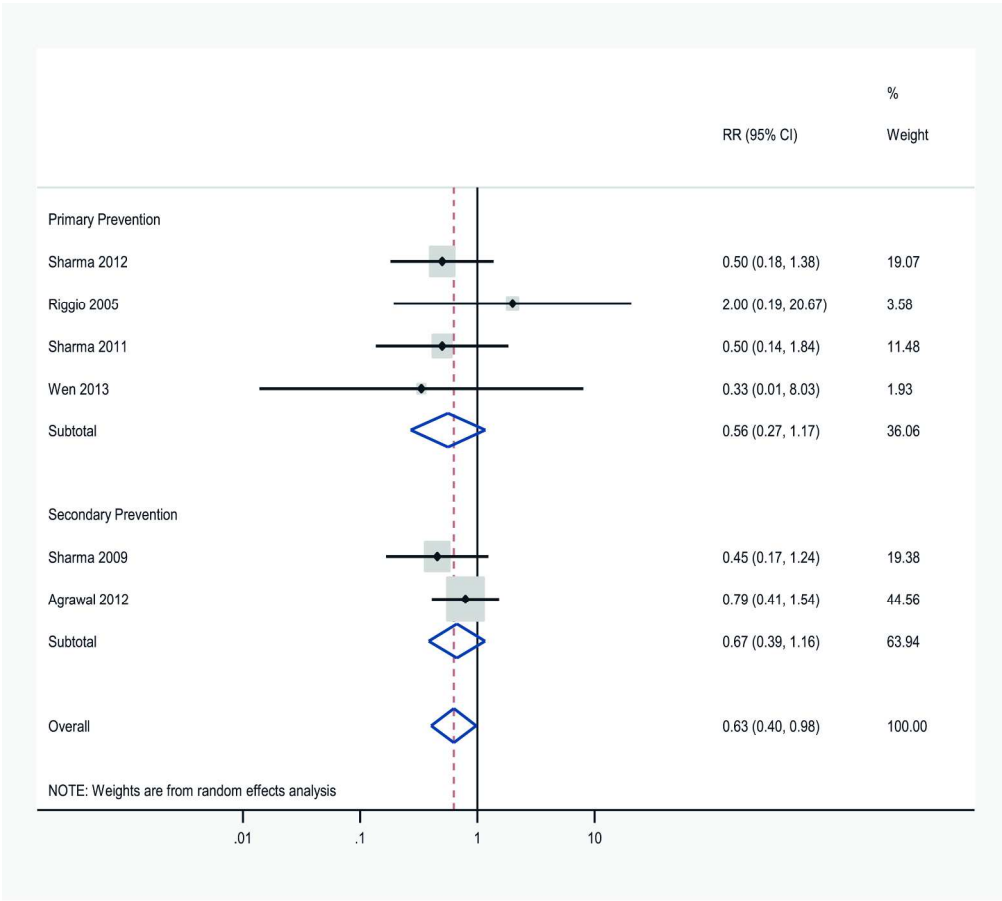

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Supplementary Table 1. Database specific search strategies used to identify randomized controlled trials on non-absorbable disaccharides for the treatment and prevention hepatic encephalopathy in patients with cirrhosis.

Database	Search terms
The Cochrane Hepato-Biliary Group Controlled Trials Register	(disaccharid* or lactulos* or lactitol*) AND (encephalopath* OR liver disease* OR cirrho*)
Cochrane Central Register of Controlled Trials (CENTRAL)	#1 MeSH descriptor: [Disaccharides] explode all trees #2 MeSH descriptor: [Lactulose] explode all trees #3 disaccharid* or lactulos* or lactitol* #4 #1 or #2 or #3 #5 MeSH descriptor: [Hepatic Encephalopathy] explode all trees #6 MeSH descriptor: [Liver Diseases] explode all trees #7 MeSH descriptor: [Fibrosis] explode all trees #8 encephalopath* or liver disease* or cirrho* #9 #5 or #6 or #7 or #8 #10 #4 and #9
MEDLINE (Ovid SP)	1. exp Disaccharides/ 2. exp Lactulose/ 3. (disaccharid* or lactulos* or lactitol*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 4. 1 or 2 or 3 5. exp Hepatic Encephalopathy/ 6. exp Liver Diseases/ 7. exp Fibrosis/ 8. (encephalopath* or liver disease* or cirrho*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 9. 5 or 6 or 7 or 8 10. 4 and 9 11. (random* or blind* or placebo* or meta-analysis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 12. 10 and 11
EMBASE (Ovid SP)	1. exp disaccharide/ 2. exp lactulose/ 3. exp lactitol/ 4. (disaccharid* or lactulos* or lactitol*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title,

	device manufacturer, drug manufacturer, device trade name, keyword] 5. 1 or 2 or 3 or 4 6. exp hepatic encephalopathy/ 7. exp liver disease/ 8. exp fibrosis/ 9. (encephalopath* or liver disease* or cirrho*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 10. 6 or 7 or 8 or 9 11. 5 and 10 12. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 13. 11 and 12
Science Citation Index Expanded	5. #4 AND #3 4. TS=(random* or blind* or placebo* or meta-analysis) 3. #2 AND #1 2. TS=(encephalopath* or liver disease* or cirrho*) 1. TS=(disaccharid* or lactulos* or lactitol*)

Supplementary Table 2. Assessment of the Risk of Bias

Domain	Bias risk assessment criteria
1. Selection bias	
Allocation sequence generation	**Low**: sequence generation achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, or throwing dice are adequate if performed by an independent person not otherwise involved in the trial. **Unclear**: the method of sequence generation was not specified. **High**: the sequence generation method was not random.
Allocation concealment	**Low:** the participant allocations could not have been foreseen in advance of, or during, enrolment. Allocation was controlled by a central and independent randomization unit. The allocation sequence was unknown to the investigators (for example, if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes). **Uncert**ain: the method used to conceal the allocation was not described so that intervention allocations may have been foreseen in advance of, or during, enrolment. **High:** the allocation sequence was likely to be known to the investigators who assigned the participants.
2. Performance and detection bias	
Blinding	**Low**: blinding was performed adequately. The lack of blinding was determined as unlikely to affect the assessment of the outcome mortality. **Unclear**: there was insufficient information to assess whether blinding was likely to induce bias on the results.

	High: no blinding or incomplete blinding, and the assessment of outcomes were likely to be influenced by lack of blinding.
3. Attrition bias	
Incomplete outcome data	**Low**: missing data were unlikely to make treatment effects depart from plausible values. The investigators used sufficient methods, such as intention-to-treat analyses with multiple imputations or carry-forward analyses to handle missing data. **Unclear**: there was insufficient information to assess whether missing data in combination with the method used to handle missing data induced bias on the results **High**: the results were likely to be biased due to missing data.
4. Reporting bias	
Selective outcome reporting	**Low:** the trial reported clinically relevant outcomes (mortality, hepatic encephalopathy, and serious adverse events). If the original trial protocol was available, the outcomes should be those called for in that protocol. **Unclear:** not all pre-defined outcomes were reported fully, or it was unclear whether data on these outcomes were recorded or not. **High:** one or more predefined outcomes were not reported.
5. For–profit bias	
	Low: the trial appears to be free of industry sponsorship or other type of for-profit support that may influence the trial design, conduct, or results. **Unclear:** no information on clinical trial support or sponsorship was available. **High:** the trial was sponsored by industry, received support in the form of lactulose, lactitol, or placebo, or received any other type of support.

6. Other bias	**Low:** the trial was free of other biases including: medicinal dosing problems or follow up (as defined below). **Unclear:** the trial may or may not have been free of other domains that could put it at risk of bias. **High:** there were other factors in the trial that could put it at risk of bias such as the administration of inappropriate treatments being given to the controls (e.g., an inappropriate dose) or follow up (e.g., the trial included different follow up schedules for participants in the allocation groups).
Overall bias assessment	**Low:** all domains were low risk of bias using the definitions described above. **High:** one or more of the bias domains were of unclear or high risk of bias.

Supplementary Table 3. Definitions and assessments of overt hepatic encephalopathy in trial publications, and the corresponding definition of hepatic encephalopathy based on recommendations in the EASL/AASLD joint guidelines[13]

Trial	Definition in trial	Definition based on classification in guidelines[13]	Assessment of hepatic encephalopathy
Elkington 1969[25]*	Chronic persistent	Persistent	• Mental status assessed using Parsons-Smith criteria; • Arterial blood ammonia concentrations; • EEG.
Simmons 1970[47]	Acute or chronic remittent	Episodic (85%) or recurrent (15%)	• Mental status assessed on a scale similar to the West Haven Criteria; • Venous blood ammonia concentrations;
Brown 1971[22]*	Chronic persistent	Persistent	• Mental status; • Blood ammonia concentrations; • EEG.
Germain 1973[26]	Chronic persistent	Persistent	• Mental status assessed using Parson-Smith criteria; • Psychometric tests; • Venous blood ammonia concentrations; • EEG.
Rodgers 1973[42]*	Chronic persistent	Persistent	• Clinical assessment of mental status; • Blood ammonia concentrations; • EEG.
Corazza 1982[23]*	Chronic persistent	Persistent	• Encephalopathy Intensity Score; • Plasma ammonia concentrations.
Heredia 1987[28]	Acute	Episodic/recurrent	• Conn score; • NCT; • Blood ammonia concentrations; • EEG.

Morgan 1987a[5]	Acute	Episodic	• PSE Sum and Index.
Morgan 1987b[6]	Chronic persistent.	Persistent.	• PSE Sum and Index.
Uribe 1987a[48]	Acute	Episodic	• PSE Sum and Index.
Uribe 1987b[49]	Chronic persistent	Persistent	• PSE Sum and Index.
Heredia 1988[29]*	Chronic persistent	Persistent	• PSE Sum and Index.
Grandi 1991[27]	Chronic	Persistent	• PSE Sum and Index modified by omitting the EEG.
Pai 1995[36]	Acute	Episodic	• PSE Sum and Index.
Jankovic 1996[32]*	Acute	Episodic	• Mental status using West Haven criteria; • NCT-A; • EEG.
Raza 2004[39]	Acute	Episodic	• Clinical scoring; • Modified PSE Sum and Index with electroencephalogram omitted and Digit Symbol test replacing NCT-A.

Footnotes

*Trial not included in the analysis of HE, because data could not be extracted on the number of participants with (or without) an overall improvement.

+ Portal-Systemic Encephalopathy (PSE) sum/index,[15] which is calculated utilizing five variables, *viz:* mental status, the presence and severity of asterixis; the NCT-A time, blood ammonia concentration; and the EEG mdf. Each variable is assigned a score of 0 (no abnormality) to 4 (severe abnormality) and the PSE index calculated as the ratio of the points scored and the maximum possible score of 28.

NCT-A: Number Connection Test-A; EEG: electroencephalogram

Supplementary Table 4. Assessment of bias in the randomized controlled trials of non-absorbable disaccharides versus placebo/no treatment included in the review.

Trial	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	For-profit funding	Overall bias assessment (mortality)*
Agrawal 2012[21]	Low	High	High	Low	Low	Low	Low
Brown 1971[22]	Unclear	Low	Low	High	High	High	High
Corazza 1982[23]	Unclear	Low	Low	Unclear	Low	Low	High
Dhiman 2000[24]	Low	High	High	Low	Low	Low	Low
Elkington 1969[25]	Unclear	Low	Low	Unclear	Low	High	High
Germain 1973[26]	Low	Low	Low	Low	Low	High	High
Grandi 1991[27]	Unclear	High	High	Low	Low	High	High
Heredia 1987[28]	Low	High	High	Low	Low	High	High
Heredia 1988[29]	Low	High	High	High	High	High	High
Horsmans 1997[30]	Low	Low	Low	Low	Low	High	High
Jain 2013[31]	Low	High	High	High	High	Low	High
Jankovic 1996[32]	Unclear	High	High	High	Low	Low	High

Li 1999[33]	Unclear	High	High	Low	Low	Low	High
McClain 1984[34]	Low	Low	Low	High	Low	High	High
Mittal 2011[35]	Low	High	High	Low	Low	Low	Low
Morgan 1987[5]	Low	Low	Low	Low	Low	High	High
Morgan 1987[6]	Low	Low	Low	Low	Low	High	High
Morgan 1989[4]	Low	High	Low	Low	Low	High	High
Pai 1995[36]	Unclear	High	Low	High	High	Low	High
Prasad 2007[37]	Low	High	High	Low	Low	Low	Low
Quero 1997[38]	Low	Low	Low	High	Low	High	High
Raza 2004[39]	Unclear	High	High	Unclear	Low	High	High
Riggio 1989[40]	Low	High	Low	Low	Low	High	High
Riggio 2005[41]	Low	High	Low	Low	Low	Low	Low
Rodgers 1973[42]	Unclear	Low	Low	High	High	High	High
Sharma 2009[43]	Low	High	High	Low	Low	Low	Low
Sharma 2011[44]	Low	High	High	Low	Low	Low	Low
Sharma 2012[45]	Low	High	High	Low	Low	Low	Low

Shi 1997[46]	Unclear	Low	Low	Unclear	High	Low	High
Simmons 1970[47]	Low	Low	Low	Low	Low	High	High
Uribe 1987[48]	Low	Low	Low	High	Low	High	High
Uribe 1987[49]	Low	Low	Low	Low	Low	High	High
Watanabe 1997[50]	Low	High	High	High	Low	Low	High
Wen 2013[51]	Unclear	High	Low	High	Low	Low	High
Xing 2003[52]	Unclear	High	High	Low	Low	Low	High
Yao 2014[53]	Unclear	Unclear	Unclear	Low	Low	Unclear	High
Zeng 2003[54]	Unclear	High	High	Low	Low	Low	High
Ziada 2013[55]	Unclear	High	Low	High	Low	Low	High

*Individual domains were assessed as low risk, unclear risk (insufficient information provided) or high risk of bias. The overall bias assessment included all domains for non-mortality outcomes and was classified as low risk of bias if all domains were assessed as such. The overall bias assessment for mortality outcomes did not include performance or detection bias. None of the included trials were classified as low risk of bias in the assessment of non-mortality outcomes. *Mortality was defined as an outcome unlikely to be influenced by lack of blinding. Accordingly, blinding was not included in the overall assessment of bias for this outcome.

Supplementary Table 5. Serious adverse events* in 24 randomized controlled trials evaluating non-absorbable disaccharides (NADs) versus placebo/no intervention for the treatment or prevention of hepatic encephalopathy in people with cirrhosis.

Treatment trials (n=18)	NADs (n=433)	Placebo/no intervention (n=386)
	n (%)	
Liver failure	1 (0.2)	2 (0.5)
Variceal bleeding	2 (0.4)	4 (1)
Mortality associated with severe liver disease	17 (4)	33 (9)
Total number of serious adverse events	20 (5)	39 (11)

Prevention trials (n = 6)	NAD (n=335)	Placebo/no intervention (n=333)
	n (%)	
Liver failure	1 (0.3)	5 (2)
Hepatorenal syndrome	6 (2)	7 (2)
Infections (pneumonia and urinary tract)	5 (1)	7 (2)
Spontaneous bacterial peritonitis	10 (3)	16 (5)
Variceal bleeding	5 (1)	14 (4)
Mortality associated with severe liver disease	17 (5)	33 (10)
Total number of serious adverse events	51 (15)	110 (33)

*Defined as any untoward medical occurrence that lead to death, were life threatening or required hospitalization or prolongation of hospitalization.