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To better understand minimal hepatic encephalopathy (MHE), a brief discussion of hepatic encephalopathy is first required. Hepatic encephalopathy is a major complication of liver cirrhosis (end-stage liver disease) and can be defined as the occurrence of confusion, an altered level of consciousness, and coma. It is considered a reversible syndrome of impaired brain function occurring in patients with advanced liver failure (Bianchi, Giovagnoli, Sasdelli, & Marchesini, 2012; Ferenci, Herneth, & Steindl, 1996). It occurs in approximately 30%–45% of patients with cirrhosis and 10%–50% of patients with a transjugular intrahepatic portosystemic shunt, which is a surgical procedure wherein a shunt is placed between the portal vein and the hepatic vein. Hepatic encephalopathy frequency has continued to increase, with a 21% increase in 2010 (Neff, Kemmer, Duncan, & Alsina (2013). In the advanced stages, hepatic encephalopathy is called hepatic coma and may ultimately lead to death. With this understanding of hepatic encephalopathy, the term “minimal hepatic encephalopathy” is defined as encephalopathy that does not lead to altered level of consciousness and coma (clinically overt cognitive dysfunction). In the absence of symptoms, only neuropsychiatric (NP) tests can detect attention and visual coordination deficits associated with MHE.

Background

Minimal hepatic encephalopathy has been characterized in the medical literature for well over 35 years (Zeegan, Drinkwater, & Dawson, 1970). Cognitive,
intellectual, and behavioral changes are important findings, as minimal encephalopathy has been demonstrated to impair quality of life and increase the risk of involvement in road traffic accidents (Bajaj, 2010). About 30%–50% of cirrhotic patients showed MHE (Goyal, Sidhu, & Kishore, 2017). There is limited data on the socioeconomic burden of MHE, but this condition is known to impair motor driving abilities.

In a recent driving simulator performance study in patients with cirrhosis, a higher proportion of subjects with MHE were categorized as unsafe drivers at baseline (16%) than subjects without MHE (7%; p = .02) and at 1-year follow-up (18% vs. 0%; p = .02). Individual and societal burden would then correlate to automobile crashes as a result of cognitive impairment related to MHE. Standard care has not been established for MHE, but probiotics, lactulose, and rifaximin have been used in several studies (Das, Dhiman, Saraswat, Verma, & Naik, 2001; Lauridsen et al., 2016). Goyal et al. (2017) conducted a prospective study of patients with cirrhosis and MHE, treated with lactulose and rifaximin for 3 months. Almost 50% of patients who became MHE negative after short-term (3 months) treatment had a relapse of MHE at 6 months follow-up. In summary, MHE is characterized by cognitive, intellectual, and behavioral changes, detected by NP tests, and may impair quality of life and safety when driving or operating machinery.

Lactulose is a common treatment of constipation and an adjunct to treatment of encephalopathy (Nursing Central, 2018). It is a nonabsorbable disaccharide and is broken down into organic acids. This acidifies the colon that allows ammonia (NH₃) to be converted to ammonium ions (NH₄⁺), thereby preventing its absorption. Subsequently, this leads to lower ammonia blood levels. Lactulose is administered at a starting dose of 25 ml every 1–2 hours until two soft or loose bowel movements (Lauridsen et al., 2016). Patients with MHE are at high risk for developing hepatic encephalopathy. Although the mechanisms causing brain dysfunction in liver failure are still unknown, metabolic factors can be detected through NP testing.

Approach to treatment of MHE depends on the severity of patients’ encephalopathic signs and symptoms. These include a worsening level of consciousness, intellectual capacity and behavior, and attention deficits. General supportive care includes providing appropriate nutritional support, avoiding dehydration and electrolyte abnormalities, and providing a safe environment (not having a patient socially isolated), as increases in blood ammonia as well as changes in normal electrolyte levels are influenced by good nutrition and adequate hydration (Cash et al., 2010). In addition, family and friends may see neurocognitive changes such as acute confusion, sleepiness, and agitation (Ferenci et al., 1996). All of these factors are indicators of worsening encephalopathy. Patients with MHE may benefit from treatment with lactulose or lactitol (a similar osmotic laxative), but the decision to treat should be individualized on the basis of the results of psychometric testing and the degree to which the encephalopathy has an impact on quality of life (Ferenci et al., 2002).

The purpose of this systematic review was to present the best available research evidence for the use of lactulose versus probiotics and l-ornithine-l-aspartate (LOLA) in the medical management of MHE. Despite the historically effective medical and surgical treatments, as well as current pharmacological advances, modalities of identification and prevention of MHE are not well described or translated into practice, as the research focus has been on hepatic encephalopathy. Recent attention has been focused on neurocognitive testing recommendations, with the goal of preventing MHE from developing into overt hepatic encephalopathy (Bass et al., 2010; Ferenci et al., 2002; Mullen, 2007).

Systematic reviews and meta-analyses on hepatic encephalopathy were found in the literature searching EMBASE, PubMed, and CINAHL (years 2002–2016); however, these are limited to very specific pharmacological agents such as probiotics, rifaximin, and non-absorbable disaccharides (including lactulose) and were focused on patients diagnosed with hepatic encephalopathy (Als-Nielsen, Gluud, & Gluud, 2004; Eltawil, Laryea, Peltekian, & Molinari, 2012). An additional meta-analysis included randomized controlled trials (RCTs) comparing the efficacy and safety of lactulose with placebo or no treatment in persons with MHE (Luo, Li, Lu, & Cao, 2011). Luo et al. (2011) concluded that lactulose reduced the risk of no improvement in NP scores, prevented progression to hepatic encephalopathy, reduced blood ammonia, and improved quality of life. Some literature reviews on diagnostic and treatment strategies for MHE are also seen in the literature but did not utilize meta-analysis or systematic review methodology.

Purpose and Research Questions
The purpose of this systematic review was to identify and synthesize the best available evidence on the effective treatment strategies for patients with MHE. This work was based on a prior systematic review protocol (Zucker & Redulla, 2014). The PICO question is as follows: In patients with MHE, what is the effect of lactulose alone in improving abnormal NP test results compared with LOLA, or probiotics, or a combination of probiotics and lactulose? More specifically, this review focuses on the following question. What is the best available research evidence for the use of lactulose in the management of MHE? Placebo was not a comparator.
Inclusion Criteria
Adult patients, 18 years and older, with the diagnosis of MHE with or without evidence of cirrhosis and who did not have hepatic encephalopathy, in both ambulatory and acute care hospital settings were included in the review. Studies that evaluated lactulose management of MHE were considered for inclusion.

Types of Interventions
Individual studies compared lactulose with no treatment, with probiotics, and with LOLA. No treatment is defined as supportive care for a patient with cirrhosis. Lactulose is a nonabsorbable disaccharide, and the standard oral dose in included studies is 30–60 ml in two to three divided doses so that patients pass two to three semisoft stools per day. We found no studies that used less than 30 ml of lactulose. Probiotics are microorganisms believed to be beneficial for gut flora health, and the oral dose is variable depending on the manufacturer ranging from 500 million to 110 billion colony-forming units two to three times per day. L-Ornithine-L-aspartate is the salt of the natural amino acids ornithine and aspartate, and the standard oral dose is 6 g three times per day. These treatments were not considered placebos but treatment options. Studies that compared lactulose with surgical procedures or antibiotic use were excluded because the purpose of this systematic review was to focus on nonpharmaceutical medical treatment.

Types of Studies
The review considered only RCTs, taking into account that treatment effects are best seen in comparing studies with the highest level of evidence. Quasi-experiments and other quantitative studies were eliminated. Several studies that were considered but excluded compared varying dosages of antibiotics or placebo comparators. Other studies measured outcomes such as critical flicker frequency (CFF), serum ammonia level, or brain size. Articles written in English were included, and publication dates were restricted between 2002 and 2016. After 2002, the medical and scientific literature began to characterize MHE by deficits in motor performance and the use of psychometric testing for diagnostic purposes (Ferenci et al., 2002; Weissenborn, Heidenreich, Giewekemeyer, Ruckert, & Hecker, 2003).

Types of Outcomes
The primary outcome for examination in this review included NP testing for cognitive function. Cognitive function in MHE is not as easily evaluated as in overt hepatic encephalopathy, as patients may not demonstrate any difficulties in activities of daily living. Mental status in patients with liver disease can be evaluated with a number of tests. But for activities involving attention, information processing, and psychomotor skills, NP testing is the gold standard. Such testing consists of two number counting tests (NCTs) (A and B) and the figure counting test (FCT). The use of these instruments is consistent with the consensus statement of the 11th World Congress of Gastroenterology (Ferenci et al., 2002). Scoring criteria suggest that an abnormal test score is $±2 SD$ from the age-matched and education-matched control subjects. Other measures of interest included objective measures of serum ammonia and subjective measures of mental status such as the Mini Mental Examination, but these tests were not consistently measured across all studies reviewed. The NCT and the FCT were the only two tests consistently measured in the selected RCTs and are considered reliable and valid for quantifying cognitive impairment in MHE specifically.

Search Strategy
The authors followed the approaches for systematic review outlined by the Joanna Briggs Institute (JBI) (2018). A three-step search strategy was undertaken. Step 1 consisted of assembling MeSH terminology and Boolean operators using key words to locate all relevant material on the topic. In Step 2, a limited search was completed in PubMed, CINAHL, and EMBASE databases using preliminary subject headings and key words. A second search was performed in Step 3 on a range of databases using all relevant subject headings and key words. The search included published studies and gray literature between 2002 and 2016, with the focus on the current medical management of MHE. Studies prior to 2002 were considered not useful or included in the current standard of care. Two additional key words, “minimal hepatic encephalopathy” and “disaccharides,” were added to the final search to more specifically address disaccharide use in MHE. Details of the search strategy are seen in Appendix A (see Supplemental Digital Content 1, available at: http://links.lww.com/GNJ/A50).

The aim of this study was to identify published randomized controlled clinical trials. Several systematic reviews and clinical guidelines were also searched for relevant studies. Various other reviews of literature were hand searched for relevant titles, and websites of the professional organizations such as the American Association for the Study of Liver Diseases (AASLD) and the Society of Gastroenterology Nurses and Associates (SGNA) were searched for additional studies. Finally, the website Open-Grey was searched, with no result using search terms noted earlier. No additional studies were found to be applicable for this review.

Methods of the Review
Citations were exported to RefWorks (ProQuest). All potential articles were retrieved and screened by title.
and abstract against inclusion criteria using two independent reviewers (D.M.Z. and R.R.). Full-text articles were retrieved and assessed as to their suitability for inclusion in the review. In addition, the reference lists for all studies that met the inclusion criteria were reviewed. Critical appraisal of the included studies was completed by two independent reviewers (D.M.Z. and R.R.) using the standardized critical appraisal instrument from JBI (see Appendix B, Supplemental Digital Content 2, available at: http://links.lww.com/GNJ/A51). Both reviewers were unanimous in their reviews. However, if a disagreement occurred, a third reviewer would have been invited to do an independent review.

Data Extraction
Data were extracted from the four articles using the standardized data extraction tool from JBI-SUMARI (see Appendix C, Supplemental Digital Content 3, available at: http://links.lww.com/GNJ/A52). Grading and extraction details can be seen in Table 2.

Data Synthesis
Data synthesis began with an examination of data analyses from all four studies. A discussion of these findings will be illustrated as reports of statistical significance, practical significance, and/or clinical significance. To that end, a combination of analyses has been completed: a meta-analysis of studies using continuous variables, a meta-analysis of studies using dichotomous variables, and a narrative synthesis of the study findings.

Results
Description of Studies
From the initial database search, 810 records were identified through database searching. Of these, 57 were duplicates, leaving 753 records screened by title and abstract. Of those, 622 were excluded because they were not research studies or were bench research studies. One hundred thirty-one full-text articles were assessed for eligibility, and 126 were excluded because of vitamin, antibiotic, and surgical comparators or the articles were informational or used descriptive methods. Of note, three articles were in the German language, with no translation resource available. A total of five studies were retained for review. The reviewers excluded one additional full-text study because it used quasi-experimental methods. Four studies were selected for the final review. Each was an RCT investigating the effect of lactulose compared with other products on change in cognitive function in those with MHE. Details outlining study exclusions can be found in Appendix D (see Supplemental Digital Content 4, available at: http://links.lww.com/GNJ/A53). The study selection process followed the PRISMA recommendations for reporting items for systematic reviews and can be seen in Figure 1.

Methodological Quality
The reviewers used the critical appraisal instrument from the JBI Meta-Analysis tool and JBI-SUMARI (see Appendix B, Supplemental Digital Content 2, available at: http://links.lww.com/GNJ/A51) to evaluate quality of the included studies. Studies were included if the assessment yielded five or greater “Yes” scores and are detailed in Table 1.

All four studies were deemed of high quality, meeting seven (Sharma, Sharma, Puri, & Sarin, 2008) and eight (Mittal, Sharma, Sharma, & Sarin, 2011; Prasad et al., 2007; Sharma, Sharma, Agrawal, & Sarin, 2012) of the 10 domains. Risk of bias was somewhat difficult to determine in two domains. Two domains could not be measured in any of the four studies. In Domain 2, there was no evidence that participants were blinded to the group assignment. This may have been a practical circumstance in two studies with more than one treatment, as dosing varies. In the two studies that compared lactulose with no treatment, taking lactulose may have been obvious to the participant, although there was no mention of blinding with placebos rather than the lack of a treatment intervention. In Domain 5, there was no evidence that those assessing the study outcomes were blinded to the treatment allocation in three of four studies and unclear in one. Blinding of researchers reduces treatment bias and confounding. In Domain 3, three of four studies showed evidence that the allocation to treatment groups was concealed from the allocator.

Baseline characteristics of enrolled study subjects in all groups were determined at baseline by the NP test to have MHE. Dosing of lactulose was consistent across studies, although endpoints varied from 1 month in one study, 3 months in two studies, and 3—12 months in the fourth.

In two studies (Mittal et al., 2011; Prasad et al., 2007), data analyses reported NP scores as a mean change in Z scores from baseline to 3 months. In the remaining two studies, the data were presented as an increase or decrease from baseline as percentages. Meta-analyses were performed and in all four studies, treatment with lactulose resulted in lowered abnormal NP scores, but probiotics and LOLA performed equally well in reducing abnormal NP scores.

Findings of the Review
Neuropsychiatric Test
The NP test is the gold standard in measuring cognitive capacity in this population and was the key outcome that measured any change in MHE after treatment in this review. The NP test is made of two common tests, NCTs

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A and B and FCT Parts A and B, and a variety of other tests such as block design test, digital symbol test, line tracing test, serial dotting test, and a picture completion test. If test results are expressed as Z scores, than $-2$ was considered abnormal. For NCT A, the patient is shown a sheet of paper with 25 numbered circles that are randomly spread over the paper. The task is to connect the circles from 1 to 25 as quick as possible. For NCT B, the circles include alternating numbers (1–13) and letters (A–L) and the patient is asked to connect numbers and letters in an alternating manner. Both test scores reflect the time required to complete the test and is reported in seconds including making error corrections (Sharma et al., 2008). Although multiple combinations of tests were used in each study, NCTs A and B were the only tests measured by all studies. Often, a set of four or more test sequences are administered and failure of two or more often indicates psychometric change. Other nonpsychometric tests also administered were the CFF (ophthalmological) and P300 (auditory) tests. In this systematic review, all included studies used NCTs A and B and the FCT; two of those additionally used the picture composition and the block design test. Two studies used different combinations of the aforementioned. A limitation of this review is that only a portion of subjects in each group completed one or more of the four-test sequences because of issues of illiteracy or unfamiliarity with Roman alphabetic notations. Details of changes in NP test results can be seen in Appendix E (see Supplemental Digital Content 5, available at: http://links.lww.com/GNJ/A54).

### TABLE 1. Assessment of Quality of Studies

<table>
<thead>
<tr>
<th>Citation</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>Q6</th>
<th>Q7</th>
<th>Q8</th>
<th>Q9</th>
<th>Q10</th>
<th>Total “Yes”</th>
</tr>
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<tbody>
<tr>
<td>Mittal et al., 2011</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>8</td>
</tr>
<tr>
<td>Prasad et al., 2007</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>U</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>8</td>
</tr>
<tr>
<td>Sharma et al., 2012</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>8</td>
</tr>
<tr>
<td>Sharma et al., 2008</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>7</td>
</tr>
</tbody>
</table>
Sample Characteristics
The total sample of the studies included in this review was 131 subjects randomized to control conditions and 315 subjects randomized to treatment conditions. The largest study had 160 study subjects (Mittal et al., 2011) and the smallest had 61 subjects (Prasad et al., 2007). For the purposes of evaluating the NP tests, a total of 240 healthy and educationally matched control subjects were used for data analysis. One RCT (Sharma et al., 2008) did not use control groups, but instead compared three treatments. All studies demonstrated an improvement in NP scores in persons with MHE following lactulose treatment.

Study Findings

Summary of Findings
GRADE Working Group’s (2015) grades of evidence were used to calculate evidence scores. All four articles were graded as high and details can be seen in Table 2.

Narrative Analysis
Of 322 cirrhotic patients in one RCT (Mittal et al., 2011), 160 with MHE underwent NP testing and then were randomized into four groups of 40: Group A received no treatment; Group B received lactulose 30–60 ml per day in divided doses resulting in two to three semisolid stools; Group C received probiotics (100 billion colony-forming units twice a day); and Group D received LOLA 6 g three times a day for 3 months. At that time, patients were reevaluated using NP testing for the presence of MHE. Tests included NCTs A and B and FCTs A and B, as well as the block design test and the picture completion test. Primary endpoints assessed included reduction in MHE at the end of therapy. The researchers calculated that a sample size of at least 23 patients in each group was required to detect a difference in reduction in MHE at 3 months at 90% power for a two-tailed log rank test. Neuropsychiatric test data were presented as means and 95% confidence intervals (CIs), and alpha was set at .05. Fisher’s exact test was performed to demonstrate reduction in MHE on an ITT basis. Improvements in NP test variations were studied by multivariate analysis of variance (MANOVA). The within-groups factor was time (0–3 months), and the between-groups factor was treatment (lactulose treatment vs. no treatment). Statistical analysis was performed with SPSS v. 10.0 software for Windows. The authors reported NP mean scores as numbers and frequencies. The CI ranges were from 20.3 to 61.4 before and from 6.7 to 35.9 after 3 months of treatment. The treatment group experienced a significant decrease in abnormal NP tests, 2.74 at baseline (95% CI [2.40, 3.08]) and 0.75 after 3 months (95% CI [2.19, 2.74]), compared with those in the no-treatment group (95% CI [2.16, 2.94]), 2.47 at baseline (95% CI [2.19, 2.74]) and after 3 months (2.55 by MANOVA for time and treatment, p = .001). Control and treatment groups’ NP scores decreased 3 months after treatment (from 30 to 20 and from 31 to 25, respectively).

A third RCT (Sharma et al., 2008) compared treatment efficacy in reducing MHE in cirrhotic patients. Of 199 cirrhotic patients, 105 were randomized into one of three groups of 35 to receive lactulose, probiotics, or both lactulose and probiotics for 1 month. There was no control group. Change in MHE was evaluated by change from baseline psychometric scores (NCTs A and B and FCTs A and B). In addition, the authors measured changes in P300ERP (auditory event-related potential). Tests were considered abnormal when the score was more than mean ± 2 SD from 50 age-matched and education-matched controls. Data were analyzed using SPSS v. 11 for Windows. Quantitative variables were analyzed using Fisher’s exact tests and ANOVA. An alpha level of p < .05 was set for statistical significance. The researchers compared lactulose with probiotics and a combination of lactulose plus probiotics in the treatment of MHE. Each of the three treatment groups had smaller final samples (Group A from 35 to 31, Group B from 35 to 31, and Group C from 35 to 30). Significant
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated Absolute Effects(^a) (95% CI)</th>
<th>Relative Effect (95% CI)</th>
<th>No. of Participants (Studies)</th>
<th>Quality of the Evidence(^b) (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neuropsychiatric test for cognitive function (NP) assessed with:</strong> NCTs A and B and FCTs A and B, block design test, picture completion test</td>
<td><strong>Risk With Usual Care, Probiotics, L-Ornithine-L-Aspartate</strong>&lt;br&gt;The mean neuropsychiatric test for cognitive function was 0.39 Change in the number of abnormal tests</td>
<td>-</td>
<td>160 (1 RCT)</td>
<td>⊕⊕⊕⊕ HIGH</td>
<td>Randomization completed by the nonclinical statistician. Groups were age- and literacy-matched. The control arm also saw increases in NP scores. Wide range of SDs.</td>
</tr>
<tr>
<td><strong>Psychometric testing (NP) assessed with:</strong> NCTs A and B, FCTs A and B if illiterate</td>
<td><strong>Risk With Lactulose</strong>&lt;br&gt;The mean psychometric testing was 2.34 Zs</td>
<td>-</td>
<td>61 (1 RCT)</td>
<td>⊕⊕⊕⊕ HIGH</td>
<td>The study was not blinded. Group assignment was concealed until after consenting. Z scores were adjusted for education. Wide range of SDs.</td>
</tr>
<tr>
<td><strong>Psychometric testing (NP) assessed with:</strong> NCTs A and B, FCTs A and B if illiterate; digit symbol test, line tracing test, and serial dotting test</td>
<td><strong>Risk With Lactulose</strong>&lt;br&gt;The mean psychometric testing was 67.5 s</td>
<td>-</td>
<td>68 (1 RCT)</td>
<td>⊕⊕⊕⊕ HIGH</td>
<td>The study was not blinded. Results of the NCT were reported in a tabular form as mean scores in seconds but reported in the narrative as percentages.</td>
</tr>
<tr>
<td><strong>Psychometric testing assessed with:</strong> NCTs A and B and FCTs A and B if illiterate;</td>
<td><strong>Risk With Lactulose</strong>&lt;br&gt;The mean psychometric testing ranged from 0 to 150 s</td>
<td>-</td>
<td>105 (1 RCT)</td>
<td>⊕⊕⊕⊕ HIGH</td>
<td>Three treatment groups with no control condition. Results of NP tests reported as percentages in narrative and seconds in tables.</td>
</tr>
</tbody>
</table>

Note. CI = confidence interval; FCT = figure connection test; MHE = minimal hepatic encephalopathy; NCT = number connection test; NP = neuropsychiatric; RCT = randomized controlled trial.

\(^a\)The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

\(^b\)GRADE Working Group grades of evidence:

**High quality:** We are very confident that the true effect lies close to that of the estimate of the effect.

**Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

**Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

**Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
improvement was seen in abnormal psychometric scores in all three groups. Minimal hepatic encephalopathy reduced equally in 51%–56% of patients treated with lactulose, probiotics, and a combination of lactulose and probiotics. Normalization of abnormal parameters occurred in 17 of 31 patients in Group A, 16 of 31 patients in Group B, and 17 of 30 patients in Group C. The researchers concluded that lactulose, probiotics, and lactulose plus probiotics are equally effective in the treatment of MHE.

The fourth RCT (Sharma et al., 2012) examined whether lactulose treatment could prevent primary hepatic encephalopathy in patients with cirrhosis, with no history of hepatic encephalopathy. The researchers calculated that a sample size of 35 patients in each arm (lactulose or no lactulose) would be required to detect a difference in 120 of 250 cirrhotic patients who never had an episode of hepatic encephalopathy and who were randomized to receive either lactulose (n = 60) or no lactulose (n = 60). Patients were tested after 3 months of treatment, although they were followed for 12 months, or if they progressed to overt hepatic encephalopathy, whichever came first. Neuropsychiatric tests included NCTs A and B, FCTs A and B, digit symbol test, line tracing test, and serial dotting test. The test score is the time required to complete the test and the time needed to correct errors. Tests were considered abnormal when the score was more than ±2 SD for the matched control scores (n = 150). Minimal hepatic encephalopathy was diagnosed if two or more of the psychometric tests were abnormal at baseline; tests were measured again at 3 months. Psychometric tests were determined abnormal when the test score was more than mean ±SD from 150 age- and education-matched controls.

In addition to the NP tests, an ophthalmological test (critical flicker test) was conducted. This test was repeated eight times, and a mean value was calculated. An abnormal score was a value of less than 38 Hz. The authors used a Mann–Whitney test for unpaired data and Wilcoxon rank sum for paired data. Numbers needed to treat and absolute risk reduction were calculated as per protocol and ITT analysis. The probability level of +.<.05 was set for significance. Group L received lactulose and Group NL received no lactulose. Patients were followed for 12 months or until patients developed overt hepatic encephalopathy. In 60 subjects assigned to Group L, five were lost to follow-up, five developed overt hepatic encephalopathy, five died, and 10 were readmitted for reasons other than hepatic encephalopathy, for a final total group size of 34. For the 60 subjects assigned to Group NL, six were lost to follow-up, four shifted to lactulose, 14 developed overt hepatic encephalopathy, 10 died, and seven were readmitted for reasons other than hepatic encephalopathy, for a final sample of 14. In Group L, lactulose reduced MHE in 21 of 31 (66%) of patients. In Group NL, nine of 36 (24%) patients recovered from MHE without any therapy. On multivariate analysis, the presence of MHE at baseline was significantly associated with development of overt hepatic encephalopathy (p = .044; 95% CI, 4.2 [1.04, 17.20]).

**Study Meta-Analysis**

The four studies were considered homogeneous from both clinical and methodological standpoints; thus, it was determined that pooling the studies in statistical meta-analysis was appropriate. Meta-analyses were performed using Review Manager 5.3 (The Cochrane Collaboration, 2014). Two studies reported data as dichotomous (Mittal et al., 2011; Prasad et al., 2007). See Figure 2 for an illustration of a Forest plot of these findings. The small squares represent point estimates for each study, with the extending lines indicating CIs. The black diamonds are plotted horizontally against a vertical line of no effect (1) either to the right (favors control) or to the left (favors the experiment) and represent the combined overall result calculated by the meta-analysis. A more stretched-out diamond represents an imprecise finding with broad CIs. The test for overall effect is an SD represented by the Z score of ±2.32. The final effect size in this table is a relative risk of 0.65 (95% CI [0.45, 0.93]), favoring the experimental group.

The other two studies reported data as continuous (Sharma et al, 2008, 2012). See Figure 3 for these findings. The Forest plot results for these studies are plotted horizontally against a vertical line of no effect (0). Small squares are point estimates for each study, with the size of the square representing the contribution of that study make to the overall summary effect. The tight and slim diamond illustrates a precise finding with a narrow CI, and this finding suggests that the intervention is effective. The Z score is 5.11 and the final effect size is −0.99 (95% CI [−1.38, −0.61]), favoring the experimental group. Overall, the results are organized by the outcome of lowered abnormal NP test scores. In all four studies, the outcome improved irrespective of treatment with probiotics, LOLA, or a combination of lactulose and probiotics compared with lactulose alone.

**Discussion**

This systematic review identified four RCTs meeting quality criteria. These studies included 446 patients with MHE. The central finding from this review suggests that treatment with lactulose, probiotics, a combination of lactulose and probiotics, or LOLA is equally effective in reducing NP signs and symptoms associated with MHE. This finding is consistent with previous studies of treatment of overt hepatic encephalopathy (Als-Nielsen et al., 2004; Eltawil et al., 2012). In addition, this finding is consistent with those reported in a 2011 systematic review (Luo et al., 2011).
but that review included three studies that compared lactulose with a placebo (vitamin B), four studies that compared lactulose with no treatment, one study that compared lactulose with supportive treatment, and one study that compared lactulose with lactose. Outcomes of interest in that study were prevention of progression to overt hepatic encephalopathy, reduced serum ammonia levels, and increased quality of life.

**Limitations**

Several studies included the same authors (B. C. Sharma, three of four studies; P. Sharma, three of four studies; and S. K. Sarin, three of four studies.) Also, the studies all came from one country, with three conducted at the G. B. Pant Hospital in New Delhi, India, and one study conducted at the Post Graduate Institute of Medical Education and Research in Chandigarh,
India. The period of intervention was 3 months in two studies, 1 month in one study, and 3–12 months in another. One study did not use a control group but used a three-treatment-group design. Across the four studies reviewed, sample sizes ranged from 61 to 160. Surprisingly, although three of the same authors were involved with three or more studies, the analyses used and reporting methods for each study were different. An additional limitation was only being able to access English language articles.

Implications for Practice and Research

Lactulose is relatively inexpensive and is as effective as LOLA and probiotics when administered to the patients with MHE to prevent development of overt hepatic encephalopathy. The NP test scores are very effective in determining changing cognitive level in both literate and illiterate populations with MHE and when administered correctly can be administered at the patient encounter. Such testing can also be administered by family members who have more frequent contact with the patient than the provider. It is recommended that future studies include similar measures and metrics for analysis, making a meta-analysis possible. Because of the diversity in treatment durations (1, 3, and 12 months), as well as application of a variety of data analyses across studies, the overall evidence was not strong for the four studies. To strengthen the current evidence, additional well-controlled RCTs are required. This includes emphasis on larger sample sizes, statistical power, and consistent treatment duration and comparison groups. A multisite RCT using the same groups, doses, and treatment duration would enhance practice recommendations.

Conclusions

All of the interventions (lactulose, probiotics, and LOLA) seemed equally effective in reducing NP test scores in MHE patients. Our review did not address other issues such as effect on quality of life, symptoms, and levels of serum ammonia, as the outcome of interest in this analysis was changes in the abnormal NP test. Final sample sizes were small, and there was evidence of geographic bias, as the same authors conducted several of the studies. Grading of the evidence resulted in mixed recommendations. Although RCTs carry a higher score, the final sample sizes for analysis were small and reporting of significant findings was varied from study to study. Our findings are consistent with a Cochrane review completed in 2004 (Als-Nielsen et al., 2004) that showed insufficient evidence to support or refute the use of nonabsorbable disaccharides for MHE.

REFERENCES


