The 46th Annual Meeting of the European Association for the Study of the Liver (EASL) took place in Berlin, Germany, from March 30 to April 3, 2011. The meeting included a number of presentations of recent studies relating to the diagnosis and treatment of hepatic encephalopathy (HE), a major complication of advanced liver disease. It is estimated that as many as 1% of the population of the United States may have cirrhosis.¹ Overt HE (OHE) occurs in approximately 30% to 45% of cirrhotic patients, while minimal HE (MHE) affects up to 80% of patients with cirrhosis.²,³ There is an increasing awareness of the debilitating effect of MHE on quality of life in general, on work performance, and on driving skills, which has led to considerable research relative to improving the diagnosis and treatment of MHE.³

In a prospective study of 122 cirrhotic outpatients by Román and colleagues, MHE was diagnosed in 42 (34.4%) patients utilizing the Psychometric Hepatic Encephalopathy Score.⁴ All patients were contacted every 3 months during the 12 months following diagnosis to determine the incidence of falls, the severity of injuries, if any, and the need for healthcare due to falling. Fifteen of 42 (35.7%) patients with MHE experienced falls vs 5 of 80 (6.15%) patients without MHE during follow-up (P<0.001). In addition, the mean number of falls per patient, the need for healthcare, the need for hospitalizations due to falls, the incidence of OHE, and mortality were higher in patients with MHE than in patients without MHE. The results are summarized in Table 1.

<table>
<thead>
<tr>
<th></th>
<th>MHE (n=42)</th>
<th>No MHE (n=80)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falls</td>
<td>35.7%</td>
<td>6.25%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean number of falls per patient</td>
<td>0.71 ± 1.5</td>
<td>0.08 ± 0.3</td>
<td>0.009</td>
</tr>
<tr>
<td>Need for healthcare due to falls</td>
<td>16.6%</td>
<td>2.5%</td>
<td>0.008</td>
</tr>
<tr>
<td>Need for hospitalizations due to falls</td>
<td>7.1%</td>
<td>0%</td>
<td>0.003</td>
</tr>
<tr>
<td>1-year probability of falls</td>
<td>46.6%</td>
<td>6.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incidence of OHE</td>
<td>33.3%</td>
<td>8.7%</td>
<td>0.001</td>
</tr>
<tr>
<td>Mortality</td>
<td>19%</td>
<td>3.7%</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Table 1. Effect of MHE on falls, incidence of OHE, and mortality.
A subset of patients (n=21) were receiving psychoactive treatment. Of these, 5 of 8 (62.5%) patients with MHE experienced falls vs 0 of 13 patients who did not have MHE (P=0.03). In the subset of patients not receiving psychoactive medications (n=101), the incidence of falls was 10 of 34 (29.4%) in patients with MHE vs 5 of 67 (7.4%) in those without MHE (P=0.03). In a multivariate analysis, MHE was the only independent predictor of falls during follow-up. The authors concluded that falls are problematic in cirrhotic patients diagnosed with MHE. The study also confirmed previous observations that MHE is associated with a higher incidence of OHE and death.

Bajaj et al reported the results of a study comparing self-assessment of driving skills (SADS) by cirrhotic patients before and after undergoing cognitive assessment and a driving simulation test. All patients self-assessed their driving skills utilizing a Likert scale from 0 to 10 and provided a driving history followed by cognitive testing and driving simulation. A SADS was reobtained after cognitive testing and driving simulation. Cognitive testing utilized the inhibitory control test (ICT), the digit symbol test, the line tracing test, the serial dotting test, the number connection tests A/B, and the block design test. Driving simulation included training, testing (outcomes measured crashes and speeding) and navigation (outcomes measured illegal turns and crashes). Among 65 cirrhotic patients (55% male; mean age 55 years; Model End-Stage Liver Disease (MELD)=9; mean driving experience 37 years), 31% reported an actual accident or moving violation in the previous year. The SADS score, however, was statistically the same for patients reporting an accident/moving violation vs those who did not report these offenses, indicating a lack of acknowledgement of their accident/moving violation problem. A diagnosis of MHE was positive for 51% utilizing ICT criteria, while 45% were diagnosed as having MHE using other tests. Driving simulator crashes correlated only with ICT performance. A decrease in SADS was observed in 40% of patients and navigation crashes (r=0.38; P=0.01) and the block design test. Driving simulation included training, testing (outcomes measured crashes and speeding) and navigation (outcomes measured illegal turns and crashes). Among 65 cirrhotic patients (55% male; mean age 55 years; Model End-Stage Liver Disease (MELD)=9; mean driving experience 37 years), 31% reported an actual accident or moving violation in the previous year. The SADS score, however, was statistically the same for patients reporting an accident/moving violation vs those who did not report these offenses, indicating a lack of acknowledgement of their accident/moving violation problem. A diagnosis of MHE was positive for 51% utilizing ICT criteria, while 45% were diagnosed as having MHE using other tests. Driving simulator crashes correlated only with ICT performance. A decrease in SADS was observed in 40% of patients and navigation crashes (r=0.38; P=0.01) and the block design test. Driving simulation included training, testing (outcomes measured crashes and speeding) and navigation (outcomes measured illegal turns and crashes). Among 65 cirrhotic patients (55% male; mean age 55 years; Model End-Stage Liver Disease (MELD)=9; mean driving experience 37 years), 31% reported an actual accident or moving violation in the previous year. The SADS score, however, was statistically the same for patients reporting an accident/moving violation vs those who did not report these offenses, indicating a lack of acknowledgement of their accident/moving violation problem. A diagnosis of MHE was positive for 51% utilizing ICT criteria, while 45% were diagnosed as having MHE using other tests. Driving simulator crashes correlated only with ICT performance.

Balzola and colleagues reported the results of a study that utilized a wheat-and-milk protein-free diet (WMPFD) in 16 patients with untreatable chronic HE awaiting liver transplant. Ten HE patients without a WMPFD served as controls. The study was based on the previous observation that the exogenous opioid peptides, β-γ-adamorphine and β-caseomorphine, were found in excess in the urine of cirrhotic patients. β-γ-adamorphine and β-caseomorphine are thought to exert a direct central morphic action, and a WMPFD has been reported to reduce blood levels of these proteins. Patients were prescribed a normoprotein WMPFD at baseline; caloric intake was evaluated according to the Harris-Benedict equation. Patients continued receiving ongoing HE medical treatments. Encephalopathy scores were determined at baseline and during follow-up. A consistent improvement in HE was seen after 4 weeks of WMPFD in 14 out of 16 patients (87%). The improvement was maintained over a 3-month observation period in these patients, while one patient continued to have light lethargy and one patient had persistent HE. Although global cognitive status improved in 14 of 16 WMPFD patients, changes in the electroencephalogram did not correlate with these changes. Only one WMPFD patient required hospitalization, while the hospitalization rate for HE was 1 to 3 per month in the control group. A rechallenge with wheat and milk resulted in immediate HE in one patient. The authors concluded that while this preliminary study needs confirmation, a WMPFD might be an adjunctive therapeutic option for patients with HE.

Elevated plasma ammonia levels associated with clinical features of cerebral edema and increased intracranial pressure are implicated in the pathogenesis of HE. L-ornithine-L-aspartate (LOLA) is a compound that lowers plasma ammonia concentrations by its ability to enhance the metabolism of ammonia to glutamine. Several randomized, controlled trials in patients with MHE have demonstrated a beneficial effect following administration of LOLA. McPhail et al studied 21 cirrhotic patients with MHE diagnosed by using Psychometry Hepatic Encephalopathy Scoring (PHES). The patients were treated with LOLA for 4 weeks. Clinical reviews, blood chemistry, PHES, and Cognitive Drug Research Scores (CDRS) were assessed at baseline and after week 4. Functional magnetic resonance imaging (fMRI) and volumetric MRI were performed; regional brain volume and neural activation change (Blood Oxygenation Level Dependent [BOLD]) were assessed. No change in the clinical or biochemical parameters was noted. The improvement in psychometric tests is summarized in Table 2.

<table>
<thead>
<tr>
<th></th>
<th>Mean Difference</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>PHES Score</td>
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<tr>
<td>CDR Score</td>
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</tr>
<tr>
<td>Speed of Memory z-Score</td>
<td>+0.6</td>
<td>0.005</td>
</tr>
<tr>
<td>Quality of Executive Memory z-Score</td>
<td>+0.4</td>
<td>0.002</td>
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Table 2. Mean changes in psychometric test scores following 4 weeks of LOLA compared to baseline.
psychometric performance. The authors conclude that improvement in HE following the administration of LOLA appears to be unrelated to improvement in cerebral edema.

Rifaximin is a minimally absorbed broad spectrum antibiotic that was recently approved for reduction in risk of overt HE recurrence in patients ≥18 years of age. Rifaximin 550 mg BID decreased the risk of breakthrough HE by 58% (P<0.0001) over 6 months in the registration trial, which involved 299 cirrhotic patients with a history of ≥2 OHE episodes and a Conn score ≥2 within 12 months prior to enrollment in the study. Mullen and associates reported results from a long-term efficacy and survival open-label study of 152 rollover patients from the registration trial and 128 new patients treated with rifaximin. The rollover patients were rifaximin (n=70) or placebo (n=82) patients who completed or withdrew from the registration trial with a Conn Score ≤2. Sixty of the 70 rifaximin treated patients from the registration trial who enrolled in the long-term follow-up remained in remission at study completion or withdrawal and were followed for up to 1008 days.

With an average exposure of 630 days, 43 (72%) of these patients did not experience breakthrough OHE; the rate of breakthrough occurrence was 0.2 events/person-years of exposure. For the 82 placebo patients from the registration trial who crossed over to open-label rifaximin, the risk of experiencing breakthrough OHE was decreased by 79% compared to their prior 6-month placebo treatment; the rate of breakthrough occurrence was 0.4 events/person-years of exposure, significantly lower than the 1.5 events/person-years of exposure during the registration trial (P<0.001). Changes in the MELD score were minimal in both the registration trial and the open-label extension, regardless of treatment. Event rates for death were similar for the placebo group and for the rifaximin group (0.2 placebo vs 0.1 rifaximin). The safety profile did not change with longer rifaximin exposure. The authors concluded that longer therapy with rifaximin is associated with continued protection from breakthrough HE with no adverse effect on expected mortality.

References

Hepatic Encephalopathy Update: Reports From the 2011 European Association for the Study of the Liver Conference

Please select the one best answer by circling the appropriate letter.

1. What percentage of patients with cirrhosis is thought to be affected with minimal hepatic encephalopathy?
   a. 20%
   b. 40%
   c. 60%
   d. 80%

2. Cirrhotic patients who are diagnosed with minimal hepatic encephalopathy are prone to:
   a. A debilitating effect on work performance
   b. A debilitating effect on driving performance
   c. Falls
   d. All of the above

3. Which of the following diets has been demonstrated to result in a consistent improvement in cirrhotic patients with chronic hepatic encephalopathy awaiting liver transplant?
   a. Wheat- and milk-protein-free diet
   b. Gluten free diet
   c. Low cholesterol diet
   d. Low carbohydrate diet

4. True or false. The improvement in symptoms in cirrhotic patients with minimal hepatic encephalopathy that is seen following the administration of L-ornithine-L-aspartate (LOLA) is related to improvement in cerebral edema.
   a. True
   b. False

5. The long-term (average exposure 630 days) administration of rifaximin to cirrhotic patients at risk for a recurrence of overt hepatic encephalopathy resulted in:
   a. A significant reduction in the event rate for death in the patients carried over from 6 months of rifaximin compared to the placebo group that was rolled over to rifaximin.
   b. Significant reductions in the MELD score in all study arms
   c. Significant reductions in the rate of breakthrough overt hepatic encephalopathy compared to rates seen with 6 months of placebo treatment
   d. All of the above statements are true
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Purdue University College of Pharmacy respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form.

**Impact of the Activity**

- Please indicate which of the following American Board of Medical Specialties/Institute of Medicine core competencies were addressed by this educational activity (select all that apply):

  - [ ] Patient care or patient-centered care
  - [ ] Practice-based learning and improvement
  - [ ] Interpersonal and communication skills
  - [ ] Employ evidence-based practice
  - [ ] Interdisciplinary teams
  - [ ] Professionalism
  - [ ] Quality improvement
  - [ ] Medical knowledge
  - [ ] System-based practice
  - [ ] Utilize informatics
  - [ ] None of the above

- The content of this activity matched my current (or potential) scope of practice.
  - [ ] No
  - [ ] Yes, please explain

- Was this activity scientifically sound and free of commercial bias* or influence?
  - [ ] Yes
  - [ ] No, please explain

* Commercial bias is defined as a personal judgment in favor of a specific product or service of a commercial interest.

**This learning objective did (or will) increase/improve my:**

<table>
<thead>
<tr>
<th></th>
<th>High Impact</th>
<th>Moderate Impact</th>
<th>No Impact</th>
<th>Not Applicable</th>
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<tbody>
<tr>
<td>Knowledge</td>
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<td>Competence</td>
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<td>Performance</td>
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<td>Patient Outcomes</td>
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</table>

**Strongly Agree** | **Agree** | **Disagree** | **Strongly Disagree** | **Not Applicable**

- The educational activity has enhanced my professional effectiveness in treating patients.
  - [ ]

- The educational activity will result in a change in my practice behavior.
  - [ ]
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• How will you change your practice as a result of participating in this activity (select all that apply)?
  - Create/revise protocols, policies, and/or procedures
  - Change the management and/or treatment of my patients
  - This activity validated my current practice
  - I will not make any changes to my practice
  - Other, please specify: ______________________________

• What new information did you learn during this activity?
  __________________________________________________
  __________________________________________________
  __________________________________________________

• Please indicate any barriers you perceive in implementing these changes.
  - Lack of experience
  - Lack of resources (equipment)
  - Lack of time to assess/counsel patients
  - Lack of consensus of professional guidelines
  - Lack of opportunity (patients)
  - Lack of administrative support
  - Reimbursement/insurance issues
  - Patient compliance issues
  - No barriers
  - Cost
  - Other ______________________________

• If you indicated any barriers, how will you address these barriers in order to implement changes in your knowledge, competency, performance, and/or patients’ outcomes?
  __________________________________________________
  __________________________________________________
  __________________________________________________

• Comments to help improve this activity?
  __________________________________________________
  __________________________________________________
  __________________________________________________

• Recommendations for future CME/CPE topics.
  __________________________________________________
  __________________________________________________
  __________________________________________________

  To assist with future planning, please attest to time spent on activity:
  I spent ______ hours on this program
REQUEST FOR CREDIT

If you wish to receive acknowledgement of participation for this activity, please fill in your contact information and fax back pages 4-7 to (973) 939-8533.

Please do not use abbreviations.
We need current and complete information to assure delivery of participation acknowledgement.

Degree (please mark appropriate box and circle appropriate degree)
☑ MD/DO ☐ PharmD/RPh ☐ NP/PA ☐ RN ☐ Other __________________________

Full Name (please print clearly)
Last Name: __________________________ First Name: __________________________  Middle Initial: __________________________

Street Address: __________________________

City: __________________________ State or Province: __________________________ Postal Code: __________________________

Phone: __________________________ Ext. __________________________ Fax: __________________________

Specialty: __________________________

E-mail Address: __________________________

Signature is required to receive statement of credit
Signature: __________________________ Date: __________________________

Attestation to time spent on activity is required

Purdue University College of Pharmacy designates this enduring material for a maximum of 1 AMA PRA Category 1 Credit(s)™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

☐ I participated in the entire activity and claim 1 AMA PRA Category 1 Credit(s)™.

☐ I participated in only part of the activity and claim _______ credits