An estimated 5.5 million people in the United States have hepatic cirrhosis\(^1\) and most patients with cirrhosis are expected to develop a degree of encephalopathy at some point during their disease. The most severe form of hepatic encephalopathy (HE), overt HE (OHE), occurs in at least 30% to 45% of patients with cirrhosis\(^2\) and is a particularly pressing problem. OHE episodes not only often require inpatient hospitalization, but also can occur without warning. For example, data collected in 2005 indicated that more than 50,000 patients required hospitalization for HE.\(^3\) Furthermore, increases in the frequency and severity of HE episodes are predictive of an increased risk of death\(^4,5\) and 1- and 3- year survival rates for patients with severe HE who are hospitalized are less than 50% and less than 25%, respectively.\(^6\) Due to the severe consequences of OHE, a great deal of emphasis has been placed on diagnosis and treatment of earlier phases of HE, referred to as minimal HE (MHE) or covert HE (CHE), which are characterized by deficits in attention, reaction time, working memory, visuoconstructive abilities, and fine motor performance. The diagnosis of MHE is based on psychometric and/or neurophysiological tests that are not widely used outside of research settings because they are time consuming, expensive, and may require experienced personnel. Once detected, however, the condition can be treated with currently available HE therapies, such as lactulose (LAC) and rifaximin (RFX), to improve quality of life,\(^7,8\) driving capacity,\(^9\) and performance on psychometric tests, including the inhibitory control test. This newsletter will review selected research related to HE reported at the Digestive Disease Week Annual Meeting, which took place in Orlando, Florida, on May 18-21, 2013.\(^10\)

### Advances in Diagnostic and Prognostic Methods in Hepatic Encephalopathy

As MHE has proven to be difficult for non-specialists to diagnose using current cognitive tests, easier, patient-administered methods that do not require specialized testing or equipment are needed to improve MHE detection rates. In the poster presentation by Nabi et al, a validated quality of life (QOL) questionnaire, the Sickness Impact Profile (SIP), as well as the gold standard cognitive battery (Number connection-A/B, Digit Symbol and Blocks) for the detection of MHE, were administered to 170 cirrhotic patients without prior OHE.\(^11\) According to standard cognitive battery results, 93 (55%) patients had MHE. Additional results indicated that a “yes” response to 54 SIP statements was found in a higher proportion of patients with MHE. The results of a regression analysis detected that age, male gender, and 8 specific SIP statements...
spanning QOL domains of alertness, eating, recreation/pastimes, emotional behavior, body care, mobility, and home management differentiated between patients with and without MHE.

**Sickness Impact Profile Statement**

"I stay away from home only for brief periods of time"

"I do not maintain balance"

"I react slowly to things said or done"

"I do not keep my attention on any activity for long"

"I act irritable or impatient with myself"

"I am not doing any of the shopping that I would usually do"

"I am not doing any of my usual physical recreation or activities"

"I am eating much less than usual"

<table>
<thead>
<tr>
<th>HESA Category</th>
<th>HESA Indicator</th>
<th>Patients, n(%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Sleep disorder/impaired sleep pattern</td>
<td>CS=0 (n=32)</td>
<td>CS=1 (n=27)</td>
</tr>
<tr>
<td>Clinical</td>
<td>Tremor</td>
<td>17 (13)</td>
<td>21 (18)</td>
</tr>
<tr>
<td>Neuropsychological</td>
<td>Amnesia of recent events</td>
<td>5 (4)</td>
<td>32 (4)</td>
</tr>
<tr>
<td>Neuropsychological</td>
<td>Impaired simple computations</td>
<td>4 (3)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Neuropsychological</td>
<td>Impaired complex computations</td>
<td>3 (2)</td>
<td>18 (4)</td>
</tr>
<tr>
<td>Neuropsychological</td>
<td>Depressions</td>
<td>17 (13)</td>
<td>13 (10)</td>
</tr>
</tbody>
</table>

Table 1. Sickness Impact Profile statements that differentiated between patients with and without MHE in a regression analysis. Patients with MHE were more likely to respond "yes" to these statements.¹¹

Furthermore, receiver operating characteristic (ROC) curve analysis demonstrated an area under the curve (AUC) value for MHE diagnosis of 0.90 with 81% sensitivity and 78% specificity with all 8 statements, age, and male gender. The study authors concluded that MHE screening strategies that do not include specialized testing could increase detection rates and therapy based on their finding that 8 patient-reported questions on the SIP were effective in screening for MHE in outpatient cirrhotic patients.

Hassanein and colleagues reported results of a study aimed at assessing the utility of the Hepatic Encephalopathy Scoring Algorithm (HESA) recently incorporated into a large, multicenter, randomized controlled trial of RFX vs placebo, as a tool for enhancing HE grading in randomized, controlled trials.¹² To accomplish this aim, the ability of HESA parameters to differentiate HE grades at baseline and post-baseline was examined in 299 cirrhotic patients with recurrent HE and in remission at enrollment (Conn score (CS) of 0 or 1) in a multicenter, multinational, placebo-controlled clinical trial that examined the efficacy of RFX for maintenance of remission from OHE. Study results indicated that 200 patients (66.9%) had a CS score of 0 at baseline and 99 patients (33.1%) had a score of 1. When assessed as a function of clinical and neuropsychological HESA indicators, significant differences were observed at baseline between patients classified as 0 or 1 on the CS.

Additionally, post-baseline measurements indicated that 18 patients progressed to a CS of 2, indicative of breakthrough HE, and that significant differences in most HESA clinical and neuropsychological indicators were observed post-baseline between those with a CS = 0 vs those with a CS = 1 and those with a CS = 0 vs those with a CS = 2. The study authors concluded that the HESA may have utility for enhancing the objectivity of HE grading in large, multicenter trials, as it is an easily administered, standardized HE grading tool with good precision in differentiating CS grades 0 and 1 and correlates well with the CS.

Two poster presentations by the same research group reported on alterations in the functional connectivity of the 14 brain region default-mode network (DMN) as a means of classifying cirrhotic patients with MHE from those without MHE.¹³,¹⁴ The between-group resting state functional MRI of 14 distinct regions of interest within the DMN were studied in 17 cirrhotic patients with MHE, 13 without MHE, and 16 healthy controls without a history of liver disease. Study results from the large-scale network analysis of the DMN revealed significant differences in connectivity between the right posterior cingulate and the left posterior cingulate as well as between the right anterior cingulate and the right precuneus (P=.004) among controls and cirrhotics with MHE and significant differences including the right inferior parietal and the left anterior cingulate (P=.006) between cirrhotics with and without MHE. No significant differences were detected between controls and cirrhotics without MHE.¹³ Additional study results demonstrated that the DMN analysis was able to differentiate members of the 3 groups with high sensitivity and specificity and positive and negative predictive values. Results of an ROC analysis also showed high AUC percentages and differentiated cirrhotics with and without MHE from healthy controls.

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...levels were strongly predictive of future HE events and that the study authors concluded that fasting plasma ammonia levels ≥1.5 x the upper limit of normal (ULN) were associated with a statistically significant, several-fold increased risk of HE events, suggesting that the relationship between ammonia and HE events was nonlinear.

Based on the results of the 2 studies, the study authors concluded that cirrhotic patients with MHE exhibit significant alteration of the brain DMN when compared to cirrhotics without MHE and healthy controls and therefore, the resting-state functional connectivity of the DMN can be used to classify MHE patients from cirrhotics without MHE with a high degree of sensitivity and specificity and may provide an objective method for diagnosis of MHE among cirrhotics.

Although the utility of using plasma ammonia levels in managing cirrhotic patients with HE has been controversial, results of a recent study of an investigational ammonia-lowering agent that significantly reduced both the proportion of patients with HE events and total HE events has spurred new research and was the topic of a poster presentation by Vierling et al. In an analysis stemming from their recent multicenter, randomized, double-blind, placebo-controlled 16-week study of glycerol phenylbutyrate (GPB) in 178 cirrhotics with ≥2 OHE events in the prior 6 months, Vierling et al analyzed fasting plasma ammonia levels at baseline and after 7 and 14 days of treatment to test the predictive value of ammonia in different ranges. Study results demonstrated that HE events were strongly correlated with ammonia levels at baseline and after 7 and 14 days of treatment and that there was no evidence of drug effect independent of ammonia on days 7 or 14 in a covariate analysis. Additional study results revealed that serum ammonia levels ≥1.5 x the upper limit of normal (ULN) were associated with a statistically significant, several-fold increased risk of HE events, suggesting that the relationship between ammonia and HE events was nonlinear.

Table 3: Sensitivity, specificity, NPV, PPV, accuracy, and area under the curve for cirrhotics with MHE vs cirrhotics without MHE, cirrhotics with MHE vs healthy subjects, and cirrhotics without MHE vs healthy subjects. AUC = area under the curve; MHE = minimal hepatic encephalopathy; NH3 = ammonia; ULN = upper limit of normal.

<table>
<thead>
<tr>
<th>Event Rate*</th>
<th>Probabilities of an Individual Having 0, 1, or Multiple HE Events During the Study*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting Plasma NH3 No. of HE Events / yr**</td>
<td>0 Events 1 Event ≥ 1 Event ≥ 2 Events</td>
</tr>
<tr>
<td>0 &lt; 1.5 x ULN</td>
<td>1.13 .017 .015 .016 .068</td>
</tr>
<tr>
<td>&gt; 1.5 x ULN</td>
<td>.005 .046 .026 .050 .272</td>
</tr>
</tbody>
</table>

Table 4. Summary of event rates and probability of HE events on study day 7; findings were similar at baseline and on day 14. All comparisons significant at P<0.01. **Annualized based on 16-wk study; MHE = minimal hepatic encephalopathy; NH3 = ammonia; ULN = upper limit of normal.

The study authors concluded that fasting plasma ammonia levels were strongly predictive of future HE events and that the effect of GPB on HE events was explained entirely by its effect on ammonia. They also stated that the risk of multiple future HE events was particularly high for patients with an ammonia level ≥1.5 x ULN, and suggested that achieving a fasting ammonia level <1.5 x ULN may be beneficial in managing patients with cirrhosis and prior HE events.

Advances in the Treatment of Hepatic Encephalopathy

In a post-hoc analysis of pooled data from a 6-month, randomized, controlled trial and a long-term, open-label trial of RFX 550 mg BID in 392 cirrhotic patients with recurrent HE, Neff et al assessed the comparative efficacy and tolerability of RFX, a minimally absorbed, gut-targeted antibiotic, alone in 40 (10.2%) patients vs RFX+LAC, a nonabsorbable disaccharide, in 352 (89.8%) patients. Study results indicated that mean model for end-stage liver disease (MELD) scores were somewhat lower in the RFX alone (10.2) group vs the RFX+LAC (13.1) group. Additional results revealed that breakthrough HE events occurred in 10% of patients in the RFX alone group vs 44.6% of patients in the RFX+LAC group, which corresponded to an 82.2% reduction in relative risk of a breakthrough HE episode (P=0.0001).

The incidence of the most commonly reported adverse events (AEs), such as nausea, abdominal pain, and ascites, was lower in patients treated with RFX alone vs RFX+LAC (47.5% vs 69.6%). The study authors concluded that RFX monotherapy was more efficacious and better tolerated than RFX+LAC combination therapy. They also noted that the baseline MELD scores were somewhat lower in the monotherapy group and that this could be considered a potential limitation of the study findings.

Although RFX has demonstrated efficacy and safety in heterogenous groups of cirrhotic patients with recurrent HE, its...
profile in specific subgroups of patients has not been examined. A poster presentation reported on the efficacy and tolerability of RFX in maintaining remission from HE in 299 cirrhotic patients with a recent history of recurrent HE but in remission at enrollment, 128 of whom had hepatitis C virus (HCV), in a 6-month, randomized, double-blind, placebo-controlled trial of RFX 550 mg BID. Study results indicated that demographic and baseline characteristics were generally similar between patients with and without HCV. Additionally, breakthrough HE events occurred in 26.2% (16 of 61) of RFX patients with HCV vs 47.8% (32 of 67) of placebo-treated patients with HCV, corresponding to relative reduction in risk of a breakthrough HE episode of 52.2% (P=.014).

The most commonly reported AEs in patients with HCV were nausea, fatigue, and peripheral edema. The study authors concluded that RFX was efficacious and well-tolerated in patients with HCV and recurrent HE, with a clinical profile similar to that observed for cirrhotic patients with other etiologies of advanced liver disease.

Summary

Of the estimated 5.5 million people in the United States with hepatic cirrhosis, most will develop a degree of encephalopathy at some point during their disease. OHE, which occurs in at least 30% to 45% of patients with cirrhosis, manifests in episodes that can occur without warning and often require inpatient hospitalization. The 1- and 3- year survival rates for patients with severe HE who are hospitalized are less than 50% and 25%, respectively and have prompted research on diagnosis and treatment of MHE and CHE. Of the Digestive Disease Week (DDW) 2013 poster presentations summarized here, 4 pertained to experiments designed to improve diagnosis of CHE through the use of the SIP as a screening tool, the HESA as a grading tool, and the resting-state functional connectivity of the DMN as a means to classify MHE patients from cirrhotics without MHE. An additional presentation explored the prognostic utility of using plasma ammonia levels in managing cirrhotic patients with HE, describing a statistically significant, several-fold increased risk of HE events in patients with serum ammonia levels ≥1.5 x ULN. Two of the summarized DDW 2013 poster presentations addressed research on the treatment of HE. Specifically, one presentation describing a post-hoc analysis of pooled data from a 6-month, randomized, controlled trial and a long-term, open-label trial of RFX 550 mg BID in 392 cirrhotic patients with recurrent HE conducted to assess the comparative efficacy and tolerability of RFX vs RFX+LAC reported that RFX monotherapy was more efficacious and better tolerated than RFX+LAC combination therapy. Additionally, a presentation that described the efficacy and tolerability of RFX in maintaining remission from HE in a subpopulation of cirrhotic patients with HCV from a 6-month, randomized, double-blind, placebo-controlled trial of RFX 550 mg BID concluded that RFX was efficacious and well-tolerated in patients with HCV and recurrent HE, with a clinical profile similar to that observed for cirrhotic patients with other etiologies of advanced liver disease.

This material was supported by an educational grant from Salix Pharmaceuticals, Inc.
References


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1. According to data collected in 2005, approximately how many patients required hospitalization for HE?
   a. 100,000
   b. 75,000
   c. 50,000
   d. 25,000

2. According to the results of a regression analysis conducted by Nabi et al, which factors differentiated patients with and without MHE?
   a. Age, female gender, and 8 specific SIP statements
   b. Age, male gender, and 6 specific SIP statements
   c. Age, female gender, and 6 specific SIP statements
   d. Age, male gender, and 8 specific SIP statements

3. In the studies by Patel et al, how many brain regions comprising the DMN were examined?
   a. 14
   b. 12
   c. 10
   d. 8

4. In the study by Vierling et al:
   a. Serum ammonia levels ≤1.5 x ULN were associated with a statistically significant, several-fold increased risk of HE events, suggesting that the relationship between ammonia and HE events was nonlinear
   b. Serum ammonia levels ≥1.5 x ULN were associated with a statistically significant, several-fold increased risk of HE events, suggesting that the relationship between ammonia and HE events was nonlinear
   c. Serum ammonia levels ≤1.5 x ULN were associated with a statistically significant, several-fold increased risk of HE events, suggesting that the relationship between ammonia and HE events was linear
   d. Serum ammonia levels ≥1.5 x ULN were associated with a statistically significant, several-fold increased risk of HE events, suggesting that the relationship between ammonia and HE events was linear

5. In the study by Neff et al:
   a. Breakthrough HE events occurred in 26.2% of RFX patients with HCV vs 47.8% of placebo-treated patients with HCV, corresponding to relative reduction in risk of a breakthrough HE episode of 55.5%
   b. Breakthrough HE events occurred in 26.2% of RFX patients with HCV vs 47.8% of placebo-treated patients with HCV, corresponding to relative reduction in risk of a breakthrough HE episode of 52.2%
   c. Breakthrough HE events occurred in 26.2% of RFX patients with HCV vs 49.8% of placebo-treated patients with HCV, corresponding to relative reduction in risk of a breakthrough HE episode of 52.2%
   d. Breakthrough HE events occurred in 36.2% of RFX patients with HCV vs 47.8% of placebo-treated patients with HCV, corresponding to relative reduction in risk of a breakthrough HE episode of 52.2%
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.

How well did this activity meet the following learning objectives?

<table>
<thead>
<tr>
<th>Learning Objective</th>
<th>Knowledge</th>
<th>Competence</th>
<th>Performance</th>
<th>Patient Outcomes</th>
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</thead>
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<tr>
<td>Recognize the debilitating effects of overt hepatic encephalopathy in patients with cirrhosis</td>
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<td></td>
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<tr>
<td>Assess the results of selected studies relating to the diagnosis and treatment of hepatic encephalopathy presented at the Digestive Disease Week 2013 Annual Meeting</td>
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</tr>
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</table>

Impact of the Activity

<table>
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<tr>
<th>Impact of the Activity</th>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
<th>Not Applicable</th>
</tr>
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<tbody>
<tr>
<td>The educational activity has enhanced my professional effectiveness in treating patients</td>
<td></td>
<td></td>
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<tr>
<td>The educational activity will result in a change in my practice behavior</td>
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</tbody>
</table>

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
  - Interdisciplinary teams
  - Employ evidence-based practice
  - 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.

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Evaluation

• 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

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Evaluation

If you wish to receive acknowledgement of participation for this activity, please complete this posttest, evaluation form, and request for credit (pages 6-9) and fax 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: __________________________________________________________________________________

Date Completed: ________________________________________________________________________________

Attestation to time spent on activity is required

[ ] I participated in the entire activity and claim 0.75 AMA PRA Category 1 Credit(s)™.  
[ ] I participated in only part of the activity and claim ______ credits  
[ ] I do not wish to claim credits