In the United States, chronic liver disease (CLD) is one of the leading causes of morbidity and mortality and affects approximately 5.5 million patients. A common and challenging complication of end-stage liver disease is hepatic encephalopathy (HE). It is well known that the spectrum of neurological and neuropsychiatric symptoms associated with HE are debilitating to the patient, can result in hospitalization, and may even impact patient survival. However, effects on patients’ activities of daily living and quality of life, economic impact, and challenges placed on family members and caregivers are infrequently topics of focus. This newsletter will provide insight into the multidimensional burden of HE.

Prevalence and Clinical Presentations
The true incidence and prevalence of HE are not fully understood because etiology and symptoms differ among patients. In addition, the definition and clinical implications of the most common form of HE, known as minimal (M) HE, are the subjects of much debate, resulting in difficulties in diagnosis. Although prevalence estimates vary, 20%-80% of patients are thought to have MHE and 30%-45% have experienced episodes of overt HE, it is recognized that the majority of patients with cirrhosis will develop HE at some point during the course of the disease. This, coupled with the fact that the prevalence of cirrhosis has significantly increased between 1996 and 2006 (Figure 1), indicates that HE may be a growing complication of liver disease.

Figure 1: Significant increase in the prevalence of cirrhosis over time. This study calculated the annual prevalence of cirrhosis, decompensated cirrhosis, and hepatocellular cancer (HCC) in a national sample of veterans diagnosed with hepatitis C between 1996 and 2006. The prevalence of cirrhosis increased from 9% in 1996 to 18.5% in 2006.
HE is caused by the inability of the damaged liver to adequately remove toxins from the body. As a result, such toxins accumulate in the bloodstream and enter the brain, causing cerebral changes and episodes of neurological dysfunction. As previously noted, the most frequent neurological disturbance of HE is referred to as MHE and is characterized by mild cognitive abnormalities that are not clinically evident, but recognizable with psychometric or neurophysiologic tests. Episodes of clinically recognizable, or overt (O) HE, can manifest as alterations in patient consciousness, intellect, personality, and neuromuscular activity. Patients who demonstrate more severe stages of HE may have persistent cognitive deficits that resemble those of Alzheimer’s disease and can even become comatose, requiring hospitalization.

Adverse Consequences on Health-Related Quality of Life and Activities of Daily Living

Several studies have demonstrated that CLD causes profound impairment on patients’ health-related quality of life (HRQoL) that is correlated to repeated hospitalizations, liver disease severity, and complications of cirrhosis. Since OHE is associated with frequent hospitalizations and increased dependence on care providers, it is no surprise that the HRQoL of these patients is adversely affected. A recent study evaluated the effect of previous bouts of OHE on HRQoL in 75 cirrhotic patients using the Short Form 36 Health Survey (SF-36). Compared to those without, patients with previous bouts of OHE had significantly worsened vitality, and social and physical functioning. These patients also had a significant worsening of both the Mental Component Summary (MCS) (38 ± 17 vs. 48 ± 21; P = .04) and the Physical Component Summary (PCS) (36 ± 14 vs. 46 ± 22; P = .03) (Figure 2). Multiple regression analysis results revealed that a history of OHE was independently related to the MCS of the SF-36. This indicates that despite complete clinical resolution of OHE, there is a persistent impairment of HRQoL.

Economic Impact

The direct costs associated with liver diseases are considered enormous. The American Gastroenterological Association, using data from the 1995 National Health Interview Survey and adjusting them to 1998, found that the annual economic burden of CLD, cirrhosis, and hepatitis C is over $2.1 billion. The largest contributor to the economic burden of advanced liver disease, with annual costs of over $1.4 billion, was inpatient hospitalizations. This estimate also includes contributions from outpatient hospital visits, emergency department visits, and physician office visits. Since these figures are based on data from 1998, it is safe to assume that the current costs of advanced liver disease are actually higher.

This study, however, does not support the relationship between MHE and HRQoL. The presence of MHE was detected in 43% of the cirrhotic patients evaluated, but only one of the eight domains of SF-36 (physical functioning) was significantly different when these patients were compared to those without MHE. Another recent study echoed this finding, reporting that SF-36 and CLDQ domains were not significantly different in patients with and without MHE. It is important to note, however, that conflicting reports exist on this topic. For instance, one study using the SF-36 demonstrated a reduction in health-related quality of life in patients with MHE, particularly in the mental health and emotional domains. Similar results, based on the SF-36, were obtained in another study performed in China.

Although data are conflicting regarding MHE and the effects on HRQoL, the presence of this disorder does matter in the daily life of a patient. In a study of 179 outpatients with cirrhosis, the sickness impact profile questionnaire was used to determine the influence of MHE on daily functioning. Impairment was detected in all 12 scales in MHE patients, with the greatest impairment in the categories of social interactions, alertness, emotional behavior, mobility, sleep/rest, work, home management, recreation, and pastimes.

Other studies that focus on specific impairments associated with HE have supported these data. For example, HE affects the sleep-wake cycle, especially causing fragmentation of sleep, sleep deprivation, and reports of drowsiness during the day, which can affect psychometric test performance and impair the ability to drive. In fact, there are recent data that suggest that about 50%–60% of patients with MHE are not fit to drive and studies have demonstrated that these patients exhibit worse driving behavior (eg, car handling, cautiousness, following road signals) and navigation skills in addition to having poorer driving outcomes (eg, traffic violations and accidents) than patients without MHE. Finally, cognitive dysfunction in MHE can impact work performance, particularly in patients in “blue collar” professions that require constant vigilance and coordination (eg, machinery operators, drivers) more than verbal and intellectual functions.

This material was supported by an educational grant from Salix Pharmaceuticals, Inc.
healthcare databases and related software tools that is a national resource of patient-level hospital care data, was recently used to estimate the contribution of HE to the direct costs of care for patients with advanced liver disease. One of these databases, the Nationwide Inpatient Sample, is the largest all-payer inpatient care database in the United States, with data from approximately 7 million hospital stays. Nationwide Inpatient Sample data, available from 1988 to 2002, were used to estimate the cost for inpatient care of HE. It is important to note that this disorder is seldom coded as a primary diagnosis and a variety of ICD-9-CM codes are used in clinical practice to classify patients with HE (e.g., alcoholic cirrhosis, nonalcoholic cirrhosis, portal hypertension, HE). Therefore, to obtain the most accurate estimate of the burden of HE, this study searched the database using several of these codes. Interestingly, the study found that for patients admitted with HE as a primary diagnosis, HE is infrequently coded as such.\textsuperscript{21}

Investigators found that the estimated total charges for HE-related hospitalizations in 2003 were over $930 million. In addition, the majority of HE patients were admitted through the emergency department and these hospitalizations were associated with a prolonged, costly length of stay (mean length of stay 5.7 days with a mean charge of $23,192 per stay). Importantly, hospitalizations for HE are on the rise, more than doubling over a 10-year period (17,266 discharges in 1993; 40,012 discharges in 2003). This has resulted in a substantial increase in aggregate hospital charges, with cumulative charges totaling approximately $7 billion from 1993 to 2003 (Figure 3).\textsuperscript{27}

![Figure 3: Trends in the total charges for hepatic encephalopathy-related hospitalizations in the United States, 1993-2003\textsuperscript{27}](image)

It is important to note that the economic impact of MHE has not been assessed because it is not associated with significant morbidity or healthcare utilization. However, as previously discussed, interference with patient functioning, social interactions and work activities translates into substantial MHE-related costs.\textsuperscript{2}

**Burden on Family Members and Caregivers**

Family members and caregivers of patients with HE often absorb the challenges of this medical condition. For instance, since screening for mental changes in early HE can be somewhat difficult, it is often family members who alert physicians to changes in the patient's mental state. Despite this, data on the socioeconomic and emotional burden of HE on the family are scarce. Bajaj and colleagues recently evaluated the emotional and financial burden of cirrhosis on patients and informal caregivers. In this cross-sectional study, 104 cirrhotic patients underwent cognitive battery, sociodemographic, and financial questionnaires. Their informal caregivers were given the perceived caregiver burden (PCB; maximum = 155) and Zarit Burden Interview (ZBI)-Short Form (maximum = 48) and questionnaires for depression, anxiety, and social support.\textsuperscript{22}

The Bajaj study demonstrated that cirrhosis places a significant financial, socioeconomic, and personal burden on not only patients, but their caregivers as well. Cirrhosis-related medical expenses affected the family and resulted in many financial sacrifices compared to previous years. The most common sacrifices included inability to save money (56%) and debt (46%). Caregivers reported suffering from various degrees of depression (28%) and anxiety (29%), which the authors attribute to the scant social support provided to these individuals. Similar to what is seen with Alzheimer's disease, the burden of severity was found to be significantly higher for spouses compared to other caregivers. Within the PCB, spouses had significantly higher disruptions of schedule ($P = .05$), personal health ($P = .002$), and feelings of entrapment ($P = .004$).\textsuperscript{28}

This study also demonstrated that cirrhotic patients with previous HE were a significantly higher burden on their caregivers compared to those without previous HE. Zarit (19 vs. 12, $P = .005$) and PCB (85 vs. 68, $P = .008$) were significantly higher in caregivers of those with severe previous HE compared to those with previous HE controlled on lactulose and those without previous HE. The results indicate that the degree of caregiver burden is proportional to the patients' cognitive dysfunction and are similar to findings seen in caregivers of patients with Alzheimer's disease, Parkinson's disease, and stroke.\textsuperscript{23,24} Caregivers of patients with previous HE experienced more severe impacts on schedules and personal health and their sense of entrapment was significantly higher (Table 1).\textsuperscript{28}

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The Multidimensional Burden of Hepatic Encephalopathy

The Clinician’s Role in Reducing the Burden of HE

As discussed in this newsletter, HE negatively impacts patients’ HRQoL and activities of daily living, caregivers’ financial, emotional, and physical well-being, and consumes billions of dollars in healthcare expenditures and challenges. The increasing prevalence of cirrhosis indicates that HE, an associated complication, may also be increasing and stresses the need for strategies to overcome this immense burden. Fortunately, with the right interventions HE is reversible. In fact, a precipitating cause can be identified and treated in the majority of patients. Medical treatments with drugs such as lactulose and rifaximin, the most common treatments for HE, are also available. Lactulose is a nondigestable disaccharide that reduces the level of nitrogen-containing compounds in the gut. Rifaximin is an oral nonsystemic antibiotic and is the only FDA-approved drug for reduction of risk of OHE.

Along with disease stabilization, improving HRQoL is receiving more attention and is becoming more important in the management of patients with cirrhosis. In fact, focus on quality and disability has proven to have a stronger impact on patients’ lives than longevity. Treating HE with lactulose has demonstrated improvements in HRQoL but there are concerns that the associated gastrointestinal side effects may lead to nonadherence in the long term that can cause subsequent HE episodes and potentially worsen HRQoL.

Sanyal and colleagues recently evaluated the effects of rifaximin on disease-specific HRQoL in patients with cirrhosis in remission from HE and a documented history of recurrent HE episodes. Patients were randomized to rifaximin 550 mg bid (N = 101) or placebo (N = 118) for 6 months and the Chronic Liver Disease Questionnaire (CLDQ) was administered every 4 weeks. Patients on rifaximin demonstrated consistent and significant improvements in HRQoL compared to patients on placebo (Figure 4). This study also found a shift toward lower HRQoL scores for the group of patients who experienced breakthrough HE and demonstrated that worsening HRQoL precedes, and may predict, an episode of breakthrough HE in patients with cirrhosis.

Seven patients (6.9%) in the rifaximin-treated group discontinued the study early due to adverse events compared to six (5.1%) patients in the placebo-treated group. Concomitant lactulose use was high, however the mean daily use was equivalent between treatment groups throughout the study, eliminating potential confounding effects. The authors emphasized the need for future studies separating the impact of lactulose from rifaximin.

### Table 1: Burden on Caregivers of Patients With and Without Previous HE

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients without previous HE</th>
<th>Patients with previous HE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burden on caregivers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zarit burden interview</td>
<td>11.5 (8.4)</td>
<td>16 (9)</td>
<td>0.016</td>
</tr>
<tr>
<td>Total perceived caregiver burden</td>
<td>65 (21.8)</td>
<td>75.4 (19.2)</td>
<td>0.015</td>
</tr>
<tr>
<td>Impact on finances</td>
<td>9.3 (3.3)</td>
<td>10.6 (4.1)</td>
<td>0.112</td>
</tr>
<tr>
<td>Sense of abandonment</td>
<td>14.6 (7.2)</td>
<td>13.8 (3.3)</td>
<td>0.45</td>
</tr>
<tr>
<td>Impact on schedule</td>
<td>11.9 (7.0)</td>
<td>16.1 (6.2)</td>
<td>0.005</td>
</tr>
<tr>
<td>Impact on personal health</td>
<td>15.6 (4.1)</td>
<td>17.8 (3.7)</td>
<td>0.006</td>
</tr>
<tr>
<td>Sense of entrapment</td>
<td>13.4 (6.5)</td>
<td>17.3 (8.3)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

Bold values signify P-values that are significant at <0.05

### Figure 4: Chronic Liver Disease Questionnaire Domain scores for rifaximin vs. placebo

Differences in least square (LS) means of time-weighted average values and corresponding 95% confidence intervals for subjects in the rifaximin vs. placebo groups are presented for the 6 CLDQ domain scores and for the overall CLDQ score. Least square mean values are illustrated with diamonds and 95% confidence intervals are illustrated with brackets to the left and right of the LS mean.

With regard to MHE, testing for this complication and subsequent therapy is not standard of care at this time. As discussed, awareness of MHE is still important for the clinician in order to help patients improve their ability to live life to the fullest. Furthermore, since there are currently no specific guidelines against preventing patients with MHE from driving, this is a topic on which the clinician needs to lead a careful discussion with patients and their families.

As demonstrated by the data presented in this newsletter, the multidimensional burden associated with HE indicates that a multidisciplinary approach to disease management is essential. Management strategies that involve psychology, social work, and medical interventions will help to alleviate the burden of HE on patients and their caregivers.

This material was supported by an educational grant from Salix Pharmaceuticals, Inc.
## The Multidimensional Burden of Hepatic Encephalopathy

### References


2. The Burden of Gastrointestinal Diseases: (need more info--author/is this a book?) Bethesda, Maryland. *American Gastroenterological Association; 2001:*41-42.


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The Multidimensional Burden of Hepatic Encephalopathy

Required with 70% passing.

1. Patients with minimal hepatic encephalopathy (MHE) may experience ______.
   a. Impairments in driving ability
   b. Alterations in consciousness
   c. Changes in personality
   d. Persistent cognitive deficits similar to those of Alzheimer’s disease

2. HE-related hospitalizations ______
   a. Cost approximately $2.1 billion in 2003
   b. Are rare since most patients are treated in the emergency department
   c. Are on the rise, having more than doubled over a 10-year period
   d. Have not been studied because HE is not associated with significant healthcare utilization

3. Which of the following statements is false?
   a. MHE is the most frequent neurological disturbance of HE and is easily diagnosed
   b. The majority of patients with cirrhosis will develop HE at some point during the course of disease
   c. The prevalence of cirrhosis has significantly increased between 1996 and 2006, indicating that the prevalence of HE may be increasing as well
   d. 30%-45% of chronic liver disease patients have experienced episodes of overt HE

4. Which of the following statements is true?
   a. Lactulose is the only FDA-approved treatment for HE
   b. In one study, patients on rifaximin demonstrated consistent and significant improvements in HRQoL compared to patients on placebo
   c. Rifaximin and lactulose stabilize the symptoms associated with HE, but have no proven benefits on HRQoL
   d. Rifaximin is a nondigestable disaccharide that reduces the level of nitrogen-containing compounds in the gut

5. According to a study by Bajaj and colleagues, _____ of patients with HE carry the highest burden compared to other caregivers.
   a. Adult children
   b. Spouses
   c. Nurses
   d. Parents
# The Multidimensional Burden of Hepatic Encephalopathy

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.

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

<table>
<thead>
<tr>
<th>High Impact</th>
<th>Moderate Impact</th>
<th>No Impact</th>
<th>Not Applicable</th>
</tr>
</thead>
</table>

- Define the prevalence and clinical presentations of hepatic encephalopathy (HE)
  - Knowledge
  - Competence
  - Performance
  - Patient Outcomes

- Analyze the effects that both minimal HE and overt HE have on health-related quality of life and activities of daily living
  - Knowledge
  - Competence
  - Performance
  - Patient Outcomes

- Discuss the economic impact of HE
  - Knowledge
  - Competence
  - Performance
  - Patient Outcomes

- Examine the burden that HE places on family members and caregivers
  - Knowledge
  - Competence
  - Performance
  - Patient Outcomes

- Determine the role of the clinician in reducing the burden of HE and investigate the multidisciplinary approach to the treatment of HE
  - Knowledge
  - Competence
  - Performance
  - Patient Outcomes

## 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.
The Multidimensional Burden of Hepatic Encephalopathy

• The educational activity has enhanced my professional effectiveness in treating patients

   Strongly Agree  Agree  Disagree  Strongly Disagree  Not Applicable

• The educational activity will result in a change in my practice behavior

   Strongly Agree  Agree  Disagree  Strongly Disagree  Not Applicable

• 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?

   ________________________________________________________________
   ________________________________________________________________
   ________________________________________________________________
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   ________________________________________________________________

• 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 7-10 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)
First Name: Middle Initial: Last Name: 

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.