CLDF
Chronic Liver Disease Foundation
Hepatic Encephalopathy Update

Primary and Secondary Prophylactic Treatment
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the sponsorship of Purdue University College of Pharmacy and the Chronic Liver Disease Foundation. Purdue University School of Pharmacy is accredited by the ACCME to provide continuing medical education for physicians.

This program is supported by an educational grant from Salix Pharmaceuticals.
Educational Objectives

- Recognize the debilitating impact of covert and overt hepatic encephalopathy (HE) in patients with cirrhosis
- Assess the results of clinical studies for the primary and secondary prophylactic treatment of HE
Two Forms of HE are Recognized

- Covert hepatic encephalopathy (CHE) affects approximately 20% to 60% of patients with liver disease
  - Has been called subclinical encephalopathy or minimal encephalopathy (MHE) in the past
  - International Society for Hepatic Encephalopathy and Nitrogen Metabolism has recently endorsed using the term covert encephalopathy
- Overt hepatic encephalopathy (OHE) occurs in:
  - 30% to 45% of cirrhotic patients
  - 10% to 50% of patients with TIPS

TIPS = transjugular intrahepatic portosystemic shunt.

Diagnosis of OHE and CHE

- Diagnosis of OHE is based on *clinical diagnosis using West Haven Criteria*

- Patients with covert HE have *no clinical signs and symptoms of overt HE*
  
  - The diagnosis of covert HE is only possible through specialized psychometric and neurological measures
  
  - No consensus on diagnostic criteria or diagnostic tests has been established

Mullen KD. *Aliment Pharmacol Ther* 2006;25(suppl 1):11-16.
Traditional Concept: Most OHE Events are Reversible

- Only those patients who succumb to the precipitating event (i.e., bleeding, infection) are not reversible.

- Patients who regain consciousness and survive a severe HE event typically seem to return to their baseline level of cognitive functioning with supportive care, or with disaccharides, or with rifaximin.

- A subset of patients with OHE continue to suffer with symptoms and are classified as chronic persistent HE that may not be reversible with medical therapy.

Frederick RT. *Clin Liver Dis* 2012;16:147-158.
Hospital Discharges Associated with HE Increased by 21% in 2010

HE = hepatic encephalopathy; ICD = International Classification of Diseases.

*Data calculated using ICD-9-CM codes 291.2 (alcoholic dementia, not elsewhere classified), 348.30 (encephalopathy, not otherwise specified), and 572.2 (hepatic coma). †Includes all listed discharge diagnoses.

Consequences of Covert HE

- Increased progression to OHE: >50% develop overt HE within 30 months\(^1\)
- Significantly diminishes quality of life\(^2\)
- Significantly diminishes working and earning capacity in “blue-collar workers”\(^2\)
- Impairs driving on structured driving tests\(^3,4\)
- Increases risk of traffic accidents and violations\(^5\)

Characterization of HE Stages

Categorization is often arbitrary and varies between raters

Simple Clinical Diagnosis

Worsening cognitive dysfunction

# West Haven Criteria for Grading Mental State in Patients With Cirrhosis

<table>
<thead>
<tr>
<th>Grade</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No abnormalities detected</td>
</tr>
</tbody>
</table>
| I     | Trivial lack of awareness  
Euphoria or anxiety  
Shortened attention span  
Impairment of addition or subtraction |
| II    | Lethargy or apathy  
Disorientation for time  
Obvious personality change  
Inappropriate behavior |
| III   | Somnolence to semi-stupor  
Responsive to stimuli  
Confused  
Gross disorientation  
Bizarre behavior |
| IV    | Coma, unable to test mental state |

Proposed Terminology for Prophylactic Treatment of HE

- Treating patients with covert HE to prevent development of a first episode is referred to as primary prophylaxis of HE.
- Preventing recurrence of HE in patients who had a previous episode of HE is referred to as secondary prophylaxis of HE.

OHE Treatment Goals

- Acute episode of HE
  - Treatment of precipitating factors
  - Improvement in mental status
  - Evaluation for liver transplant

- Out-patient management after an episode of HE
  - Prevention of recurrent episodes of HE
  - Improvement of daily functioning
  - Evaluation for liver transplant

Bajaj JS. *Aliment Pharmacol Ther.* 2010;31:537-547.
Secondary Prophylaxis of HE: Rifaximin vs Placebo

**Rifaximin 550 mg BID for 6 mo (n=140)**

- Discontinued n=52 (37%)
  - Breakthrough HE: n=28
  - Adverse event: n=8
  - Death: n=6
  - Patient request: n=6
  - Exclusion criteria: n=1
  - Other: n=3

- Completed Study n=88

**Placebo for 6 mo (n=159)**

- Discontinued n=93 (58%)
  - Breakthrough HE: n=69
  - Patient request: n=9
  - Adverse event: n=7
  - Death: n=3
  - Exclusion criteria: n=3
  - Other: n=2

**Randomization 1:1 N=299 (Randomized Controlled Trial)**

- Completed Study n=88

Rifaximin Treatment in HE: Time to First Breakthrough Episode (Primary End Point)

Patients (%)

Days since randomization

Hazard ratio with rifaximin, 0.42 (95% CI, 0.28-0.64)

P < .001

58% Reduction of HE

Probability of Developing HE in Patients Receiving Prophylactic Lactulose vs Placebo

Probability of hepatic encephalopathy vs follow-up in months

Patients at risk*

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients at Risk</th>
<th>Values in Parentheses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactulose</td>
<td>61</td>
<td>60(1) 59(2) 58(3) 51(8) 45(9) 38(11) 28(12) 10(12) 7(12) 1(12)</td>
</tr>
<tr>
<td>Placebo</td>
<td>64</td>
<td>62(1) 59(4) 50(13) 37(24) 33(27) 28(27) 19(29) 13(30) 8(30) 4(30)</td>
</tr>
</tbody>
</table>

*Values in parentheses indicate the cumulative number of subjects who developed HE.

Most Patients are Not Receiving Prophylactic Therapy to Prevent Recurrence

• Subset of national claims for medical and hospital activity, Jan 2009 to Dec 2011, ICD-9 code 572.2 and filled prescriptions for rifaximin, lactulose, or rifaximin + lactulose

<table>
<thead>
<tr>
<th></th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible Patients Identified (n)</td>
<td>13,623</td>
<td>15,529</td>
<td>16,328</td>
</tr>
<tr>
<td>Patients with Inpatient Claims (%)</td>
<td>89.2%</td>
<td>87.8%</td>
<td>86.4%</td>
</tr>
<tr>
<td>Patients Receiving Ongoing Treatment (%)</td>
<td>39.7%</td>
<td>37.7%</td>
<td>36.1%</td>
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Primary Prophylactic Therapy: MHE Treatment Goals

- Goals of primary prophylactic therapy
  - Delay progression to overt HE
  - Improve quality of life
  - Maintain employment status
  - Preserve driving privilege

Lactulose for Primary Prophylaxis of Overt HE in Cirrhotic Patients: Results

Lactulose Improves Health-related QoL in Patients With MHE

Rifaximin vs Placebo: Reversal of MHE

Patients Showing Reversal of MHE (%)

<table>
<thead>
<tr>
<th>Duration of Treatment</th>
<th>Placebo</th>
<th>Rifaximin</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Weeks</td>
<td>18%</td>
<td>57%</td>
</tr>
<tr>
<td>8 Weeks</td>
<td>20%</td>
<td>76%</td>
</tr>
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</table>

$P < .0001$

Rifaximin Improves Health-related QoL in Patients With MHE

Long-held Tenet Now in Question: Are OHE Events Reversible?

- Traditional concept: Most OHE events are potentially reversible

- Neuropathologic characteristics found in brains of patients with HE at autopsy suggest that the concept of complete reversibility requires more in-depth analysis
Conclusions

- OHE may not be reversible and has considerable morbidity
- CHE often leads to OHE and also has considerable morbidity
- Prophylaxis of CHE may decrease rate of OHE and improve symptoms
- Prophylaxis of OHE with lactulose alone has a high failure rate and rifaximin is effective
Thank you for your participation

Please check back to the Chronic Liver Disease Foundation website frequently as updates will become available

www.chronicliverdisease.org