Chronic Liver Disease Foundation
The Importance of Diagnosing Covert Hepatic Encephalopathy
Program Disclosure

- 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

• Describe the various tests used to diagnose covert hepatic encephalopathy and the difficulty of using these tests in the office-based setting

• Discuss the benefits of primary prophylactic therapy for covert hepatic encephalopathy

• Assess the efficacy of agents currently used as primary prophylactic therapies for covert hepatic encephalopathy
Complications of Cirrhosis: Focus on Covert Hepatic Encephalopathy

- Primary complications include:
  - Ascites
  - Jaundice
  - Variceal hemorrhage
  - Hepatic encephalopathy

- Other complications that can occur include:
  - Spontaneous bacterial peritonitis
  - Hepatic hydrothorax
  - Hepatorenal syndrome
  - Portopulmonary hypertension
  - Hepatocellular carcinoma
  - Portal vein thrombosis
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 hepatic 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.

Mullen KD, Prakash RK. *Clin Liver Dis* 2012;16:91-93,
Characterization of HE Stages

- **Normal**
- **Covert HE**

Categorization is often arbitrary and varies between raters.

**Overt HE Stages**
- I
- II
- III
- IV (coma)

Simple Clinical Diagnosis

Worsening cognitive dysfunction

Covert Hepatic Encephalopathy

- Significantly diminishes quality of life
- Significantly diminishes working and earning capacity in blue-collar workers
- Increased progression to OHE
- Impairs driving on structured driving tests
- Increases risk of traffic accidents and violations

Diagnosis of Covert HE

• Patients with covert HE have no clinical signs and symptoms of overt HE

  – The diagnosis of covert HE is only possible through specialized psychometric or neurological measures

  – No consensus on diagnostic criteria or diagnostic tests has been established

Mullen KD. *Aliment Pharmacol Ther* 2006;25(suppl 1):11-16.
Do we have an effective, easy-to-use testing system for the detection of CHE by independent nonacademic center–based physicians?
## Diagnostic Methods for Minimal Hepatic Encephalopathy (MHE)

<table>
<thead>
<tr>
<th>Methods</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formal neuropsychologic assessment</td>
<td>Established and well-recognized clinical significance</td>
<td>• Expensive&lt;br&gt;• Time consuming</td>
</tr>
<tr>
<td>Short neuropsychologic batteries</td>
<td>• Easy to administer in office setting&lt;br&gt;• Inexpensive&lt;br&gt;• Rapid results&lt;br&gt;• High sensitivity for discerning minimal HE from other encephalopathies</td>
<td>• Test often copyrighted&lt;br&gt;• Limited access</td>
</tr>
<tr>
<td>Computerized tests (CFF, ICT, reaction times, etc)</td>
<td>• Easy to apply</td>
<td>• Limited data on diagnostic significance&lt;br&gt;• Require standardization</td>
</tr>
<tr>
<td>Neurophysiologic tests (EEG, spectral EEG, P300)</td>
<td>• Allows for objective repeat testing</td>
<td>• Equipment&lt;br&gt;• Limited data on diagnostic significance</td>
</tr>
</tbody>
</table>

CFF - critical flicker frequency; ICT - inhibitory control test; EEG - electroencephalography; P300 - auditory event-related evoked potential.

CNS Vital Signs as Screening Tool for MHE

• CNS Vital Signs (CNSVS) is a widely available and easy to use computerized psychometric test battery
  – Available online at www.cnsvs.com

• Detects abnormal performance in the following domains:
  – Processing speed
  – Verbal memory
  – Executive function
  – Reaction time
  – Cognitive flexibility
  – Complex attention

• Has been used to assess neurocognitive function in several other medical and psychiatric conditions

CNS Vital Signs as Screening Tool for MHE

- Cirrhotics screened to exclude OHE
- Subjects received PHES test battery (DST, NCT-A, NCT-B, SDT) and the CNSVS test battery
  - Time required for the two testing systems was similar
- Matched healthy controls were used to obtain PHES normative data
- CNSVS has composite domain-based scoring system
  - Scores in individual domains calculated based on number of SDs below age-adjusted mean
  - MHE diagnosed when total score is \( \geq 6 \) SD below the mean across the 6 domains
CNS Vital Signs as Screening Tool for MHE

- 100 cirrhosis subjects and 110 controls prospectively enrolled in study

- High correlation observed between CNSVS and PHES total scores
  - 0.60 (\(P<0.001\), 95% CI 0.45 - 0.74)

- CNSVS able to diagnose MHE with 85% sensitivity and 64% specificity
  - AUC = 0.74 (\(P<0.001\), 95% CI 0.63 - 0.85)

- CNSVS is a widely accessible, reliable, sensitive and convenient psychometric testing system for the diagnosis of MHE--results available immediately after the test

Stroop Smartphone App as Screening Tool for MHE

• Stroop app has 2 settings:
  – Off: Subject identifies colors presented without words
  – On: Subject identifies colors of words written in discordant colors (e.g., “green” is written in blue color)

• Each run has 10 stimuli; a mistake ends the run immediately

• 2 training runs given for both settings

• Actual task run until 3 correct runs achieved

• Output: Time needed to complete the correct runs and number of trials needed to achieve 3 correct runs
The Stroop Effect

• The Stroop effect is the finding that naming the colors without words is easier and quicker than naming colors of words written in discordant colors.

Stroop Smartphone App as Screening Tool for MHE

- Cirrhotics with/without overt hepatic encephalopathy (OHE) and age/education-matched healthy controls tested using the psychometric hepatic encephalopathy battery (PHES score $<-6 =$ minimal hepatic encephalopathy [MHE]) and the iPod Stroop app

- Total time in Stroop off state $>45.5$ seconds had highest AUC and sensitivity for MHE diagnosis

- Stroop Smartphone Testing/training time was $<6$ minutes
### Stroop Smartphone App as Screening Tool for MHE

<table>
<thead>
<tr>
<th></th>
<th>Control (n=47)</th>
<th>All cirrhotics (n=86)</th>
<th>Cirrhotics without OHE (n=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MHE (n=38)</td>
<td>no MHE (n=48)</td>
<td>MHE (n=23)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>no MHE (n=35)</td>
</tr>
<tr>
<td>Stroop off time (sec)</td>
<td>35.5 ± 5.2</td>
<td>57.0 ± 13.1*†</td>
<td>41.3 ± 7.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50.8 ± 10.9*†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>40.6 ± 6.8</td>
</tr>
<tr>
<td>Stroop on time (sec)</td>
<td>43.2 ± 6.5</td>
<td>71.3 ± 20.7*†</td>
<td>50.2 ± 9.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>62.5 ± 13.6*†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>49.2 ± 9.5</td>
</tr>
<tr>
<td>No. of trials for 3 correct off (median)</td>
<td>3</td>
<td>3.5*</td>
<td>3†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>No. of trials for 3 correct on (median)</td>
<td>3</td>
<td>4*†</td>
<td>3</td>
</tr>
</tbody>
</table>

*P<0.05 compared to controls; †P<0.05 compared to no-MHE

Therapy for Covert Encephalopathy is Effective
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


Median follow-up 12 months

- MHE at Baseline
  - Lactulose: 32/60 (53%)
  - No Lactulose: 36/60 (60%)
  - P = 0.29

- Develop OHE
  - Lactulose: 6/55 (11%)
  - No Lactulose: 15/50 (30%)
  - P = 0.02

- Died
  - Lactulose: 5/55 (9%)
  - No Lactulose: 10/50 (20%)
  - P = 0.16
Lactulose Improves Cognitive Functions in Patients With MHE

- Patients randomly assigned to receive lactulose in a dose of 30-60 ml in 2 or 3 divided doses so that patients passed 2-3 semisoft stools/day or no treatment in a nonblinded design.

<table>
<thead>
<tr>
<th></th>
<th>No Treatment</th>
<th>Lactulose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (n=30)</td>
<td>3 Months (n=20)</td>
</tr>
<tr>
<td>Mean number of abnormal NP test results*</td>
<td>2.47</td>
<td>2.55</td>
</tr>
<tr>
<td>Number of patients with MHE</td>
<td>30</td>
<td>18</td>
</tr>
<tr>
<td>Development of overt HE</td>
<td>--</td>
<td>2</td>
</tr>
</tbody>
</table>

*Patients were administered 6 tests: NCT A, NCT B, FCT A, FCT B, picture completion, and block design tests.

Lactulose Improves Health-related QoL in Patients With MHE

## Rifaximin Improves Cognitive Functions in Patients With MHE

<table>
<thead>
<tr>
<th></th>
<th>Rifaximin* (n=49)</th>
<th>Placebo (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Improvement</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- at 2 weeks</td>
<td>28/49 (57.1%)†</td>
<td>8/45 (17.8%)</td>
</tr>
<tr>
<td>- at 8 weeks</td>
<td>37/49 (75.5%)‡</td>
<td>9/45 (20%)</td>
</tr>
<tr>
<td><strong>Mean number of abnormal NP tests‡</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- baseline</td>
<td>2.35 (2.17-2.53)</td>
<td>2.31 (2.03-2.59)</td>
</tr>
<tr>
<td>- at 2 weeks</td>
<td>1.29 (1.02-1.56)</td>
<td>2.03 (1.74-2.31)</td>
</tr>
<tr>
<td>- at 8 weeks</td>
<td>0.81 (0.61-1.02)</td>
<td>1.97 (1.69-2.25)</td>
</tr>
</tbody>
</table>

*1200 mg/day for 8 weeks.
†P<0.0001, rifaximin compared to placebo.
‡5 NP tests (2 number and figure connection, picture completion, digit symbol, block design).

Rifaximin Improves Health-related QoL in Patients With MHE

- Patients randomized to receive placebo or rifaximin 1200 mg/day for 8 weeks

Mean SIP Score

<table>
<thead>
<tr>
<th>Category</th>
<th>Baseline (n=42)</th>
<th>8 Weeks (n=37)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep/Rest</td>
<td>P=0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Psych</td>
<td>P=0.007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Physical</td>
<td>P=0.050</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home Mgmt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rec/Pastimes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eating</td>
<td></td>
<td></td>
<td>P=0.00</td>
</tr>
<tr>
<td>Total SIP</td>
<td></td>
<td></td>
<td>P=0.00</td>
</tr>
</tbody>
</table>

Rifaximin Improves Driving Simulator Performance

- Trial involved driving and navigation simulation at baseline
- Patients were randomized to rifaximin 550 mg or placebo BID
- Driving simulation tests repeated on the 8-week visit

<table>
<thead>
<tr>
<th></th>
<th>Rifaximin (n=21)</th>
<th>Placebo (n=21)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved cognitive tests</td>
<td>91%</td>
<td>61%</td>
<td>.02</td>
</tr>
<tr>
<td>Reduced total driving errors</td>
<td>76%</td>
<td>33%</td>
<td>.013</td>
</tr>
<tr>
<td>Reduced speeding tickets</td>
<td>81%</td>
<td>33%</td>
<td>.005</td>
</tr>
<tr>
<td>Reduced illegal turns</td>
<td>62%</td>
<td>19%</td>
<td>.012</td>
</tr>
<tr>
<td>Reduced collisions</td>
<td>43%</td>
<td>33%</td>
<td>.751</td>
</tr>
</tbody>
</table>

Conclusions

• Computer-based diagnostic tests for CHE are now available that are appropriate for use in the office-based setting

• Both lactulose and rifaximin are effective therapies that can:
  
  – Delay progression to overt HE
  
  – Improve quality of life for those diagnosed with CHE