The Chronic Liver Disease Foundation Presents

2010 HEPATOLOGY

Current Perspectives on Chronic Liver Disease

The Chronic Liver Disease Foundation Presents

2010 HEPATOLOGY
Current Perspectives on Chronic Liver Disease

Overt Hepatic Encephalopathy (OHE): A significant event

Accredited by:
PURDUE UNIVERSITY

Sponsored by:
CLDF
Chronic Liver Disease Foundation

Importance of Overt Hepatic Encephalopathy

- Associated with poor prognosis
- Retrospective review of 111 cirrhotic patients following first episode of acute OHE:
  - 82 (74%) died
  - Survival probability
    - 42% at 1 year
    - 23% at 3 years

Bustamante J et al. J Hepatol. 1999;30(5):890-895.

Diagnosis: OHE

- Clinical recognition
- Presumption that cirrhosis is present
- Exclusion of alternative causes
- Identification of precipitating factors

Adapted from:
Mullen KD. Semin Liver Dis. 2007;27(suppl 2):3-9.
Lawrence KR, Klee JA. Pharmacotherapy. 2008;28(8):1019-1032.

Neurologic Manifestations of OHE

Common
• Confusion or coma • Asterixis • Loss of fine motor skills • Hyper-reflexia • Day/night reversal • Occasionally slow,monotonous speech

aSeizures seen primarily in type A HE.

Mullen KD. Semin Liver Dis. 2007;27(suppl 2):3-9.

Treatment of OHE

Management of OHE

- Acute HE in patients with cirrhosis is reversible in the majority of patients
- A precipitating cause of OHE, rather than worsening of hepatocellular function can be identified in most episodes
- Management of the precipitating events typically leads to prompt improvement
- Clinicians should simultaneously identify and resolve precipitating events while instituting pharmacologic therapy

Ferenci P. Semin Liver Dis. 2007;27(suppl 2):10-17.

Treatment Goals for OHE

- Supportive care
- Remove precipitating factors
- Correct electrolyte abnormalities
- Cleanse gut

Blei AT et al. Am J Gastroenterol. 2001;96(7):1968-1976.

Treatment Options for OHE

- Reduce nitrogenous load arising from the gut
  - Bowel cleansing
  - Non-absorbable disaccharides (lactulose)
  - Antibiotics (rifaximin, metronidazole)*

Adapted from Blei AT et al. Am J Gastroenterol. 2001;96(7):1968-1976.

Treatment Options for OHE Lactulose

- Lactulose is metabolized by the bacteria in the colon to short chain fatty acids which lowers the colonic pH to about 5.0. Acid pH favors formation of non-absorbable NH4 from NH3
  - Hastens colonic transit
- Side effects are dose related

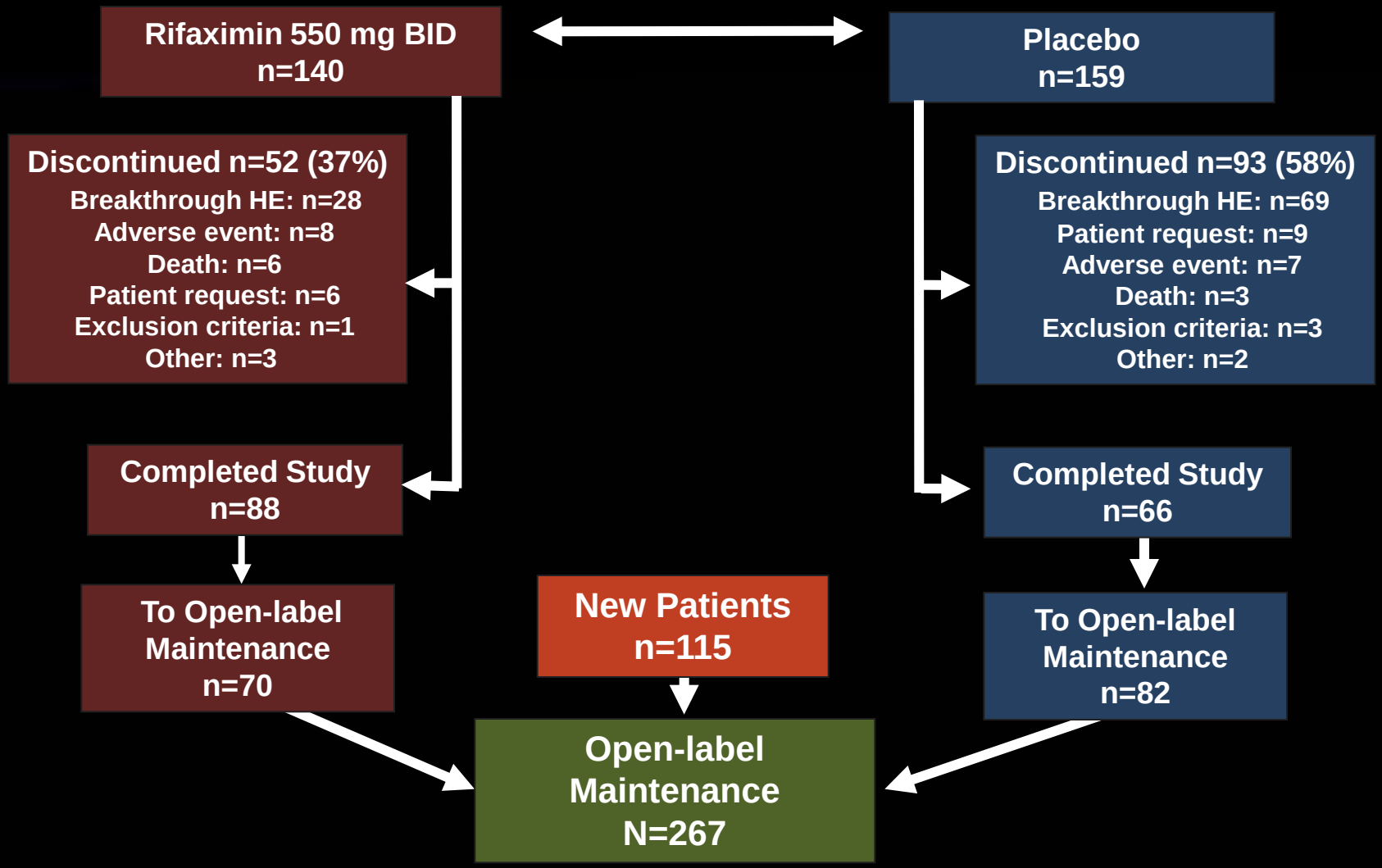
Ferenci P. Semin Liver Dis. 2007;27(suppl 2):10-17.

Rifaximin

- Oral minimally absorbed antibiotic
- Broad-spectrum activity against aerobic and anaerobic bacteria
- No dosing adjustment required in patients with liver disease or renal insufficiency
- 550 mg twice daily

Bass NM. Semin Liver Dis. 2007;27(suppl 2):18-25.
Mullen KD et al. Semin Liver Dis. 2007;27(suppl 2):32-47.

Rifaximin Treatment in HE



Bass NM et al. N Engl J Med 2010;362:1071-1081

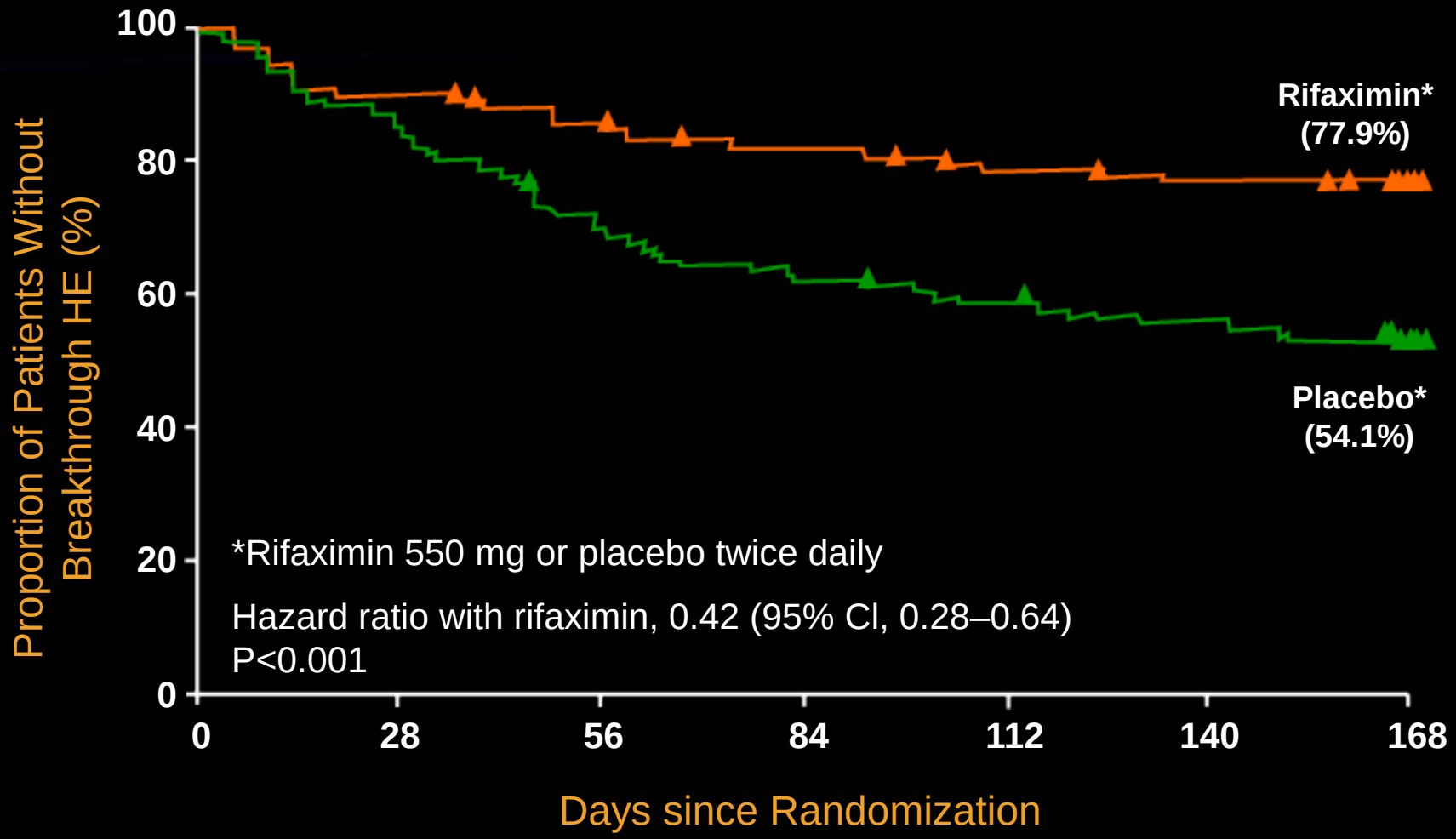
Rifaximin Treatment in HE: Lactulose Use at Baseline and During Study

	Rifaximin (n=140)	Placebo (n=159)
Lactulose use at baseline—no (%)*	128 (91.4%)	145 (91.2%)
Lactulose use during study—no (%)*	128 (91.4%)	145 (91.2%)

*During the study, 3 patients who had been receiving lactulose discontinued the therapy and another three patients started lactulose (1 in the rifaximin group and 2 in the placebo group)

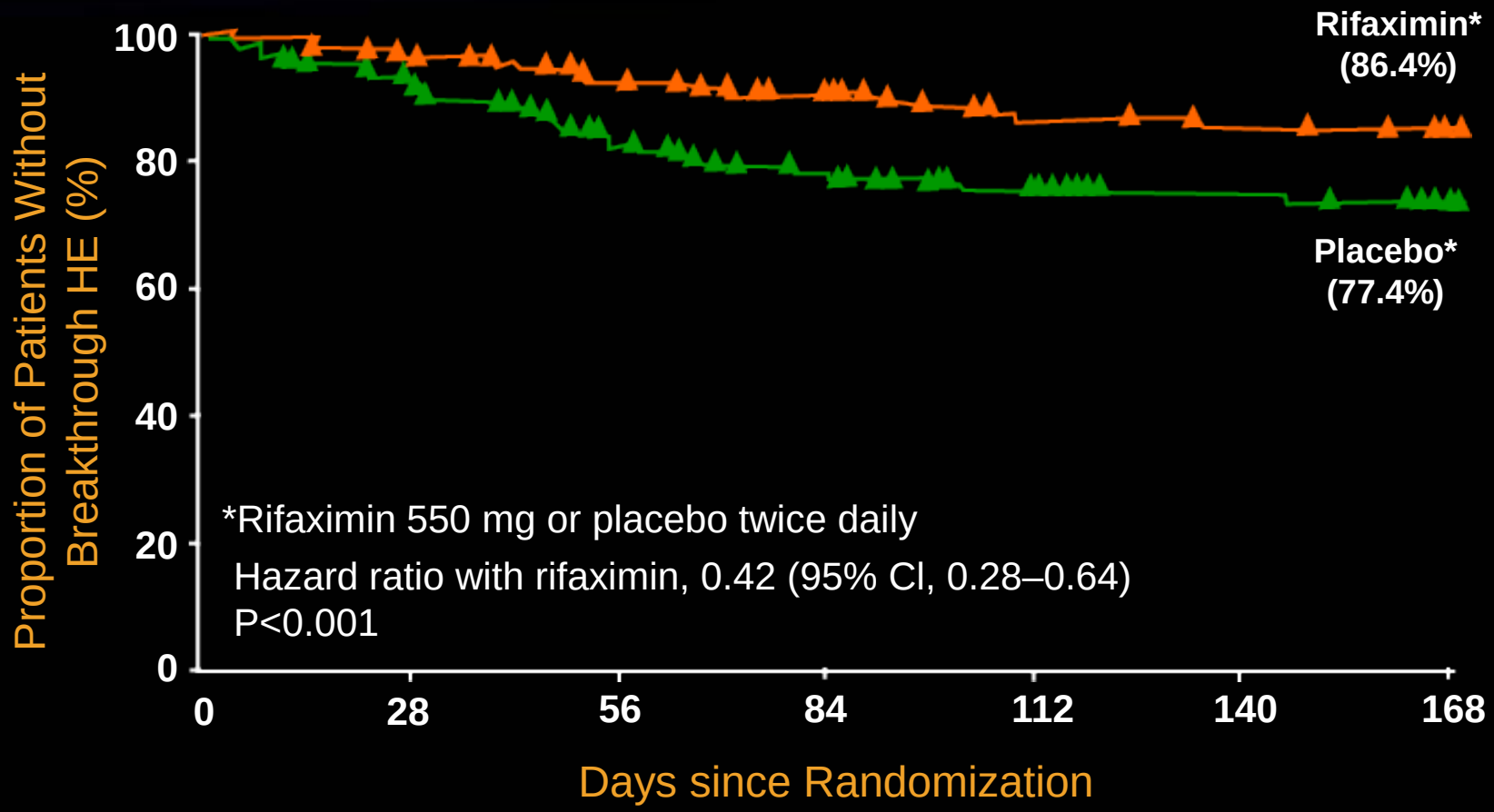
Bass NM et al. N Engl J Med 2010;362:1071-1081.

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



Bass NM et al. N Engl J Med 2010;362:1071-1081.

Rifaximin Treatment in HE: Time to First HE Related Hospitalization (Key Secondary End Point)



Bass NM et al. N Engl J Med 2010;362:1071-1081.

Summary

- Rifaximin plus lactulose achieved excellent results across a broad spectrum of patients
- Side effects from the use of rifaximin plus lactulose were no different than lactulose alone

Minimal Hepatic Encephalopathy (MHE)

Importance of Minimal Hepatic Encephalopathy (MHE)

- Identified in 60% of patients with cirrhosis[1]
- Diminished quality of life[2]
- Diminished working and earning capacity[3]
- Impairs driving/increases traffic accidents

1. Poordad FF. Aliment Pharmacol Ther. 2006;25(suppl 1):3-9.
2. Groeneweg M et al. Hepatology. 1998;28(1):45-49.
3. Romero-Gómez M et al. Am J Gastroenterol. 2001;96(9):2718-2723.
4. Wein C et al. Hepatology. 2004;39(3):739-745.
5. Watanabe A et al. Metab Brain Dis. 1995;10(3):239-248.
6. Bajaj JS et al. Am J Gastroenterol. 2007;102(9):1903-1909.

A variety of psychometric tests are available to assist in the detection of MHE

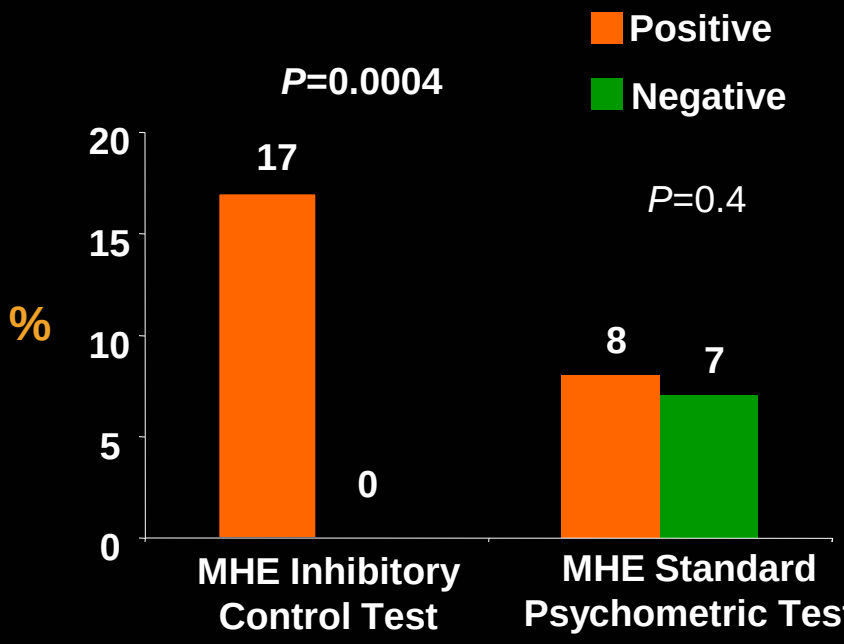
Methods
Formal neuropsychologicassessment
Short neuropsychologic batterie
Computerized tests (CFF, ICT, reaction times, etc)
Neurophysiologic tests (EEG, spectral EEG, P300)

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

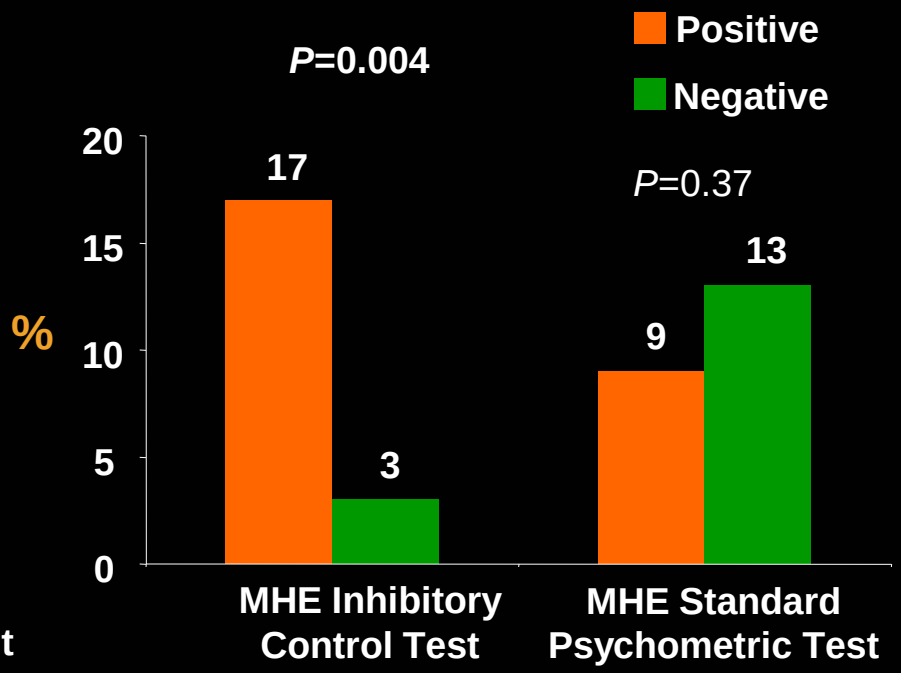
Adapted from Mullen KD et al. Semin Liver Dis. 2007;27(suppl 2):32-47.

Minimal Hepatic Encephalopathy (MHE) Is Associated With Motor Vehicle Crashes: Predictive Accuracy of Diagnostic Testing

Percentage of patients with crashes by SELF-REPORT according to MHE status and diagnostic test (n=120)



Percentage of patients with crashes by DOT according to MHE status and diagnostic test (n=167)



Bajaj JS et al. Hepatology. 2009;50(Issue S4):461A-462A.

Summary

- HE is common in the cirrhotic patient
- Increases risk of traffic accidents due to neurologic manifestations
- Increasing interest in the roles of rifaximin/lactulose in the treatment of these patients

Rifaximin and HE: Side Effects Similar to Placebo

- The incidences of adverse events did not differ significantly between the two study groups ($p>0.05$ for all comparisons)

	Adverse Events Reported in ≥10% of Patients in Either Study Group	
Event	**Rifaximin (n=140)**	**Placebo (n=159)**
Any event, n (%)	112 (80.0)	127 (79.9%)
Nausea	20 (14.3)	21 (13.2)
Diarrhea	15 (10.7)	21 (13.2)
Fatigue	17 (12.1)	18 (11.3)
Peripheral edema	21 (15.0)	13 (8.2)
Ascites	16 (11.4)	15 (9.4)
Dizziness	18 (12.9)	13 (8.2)
Headache	14 (10.0)	17 (10.7)

Bass NM et al. N Engl J Med 2010;362:1071-1081.