

Introduction

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Most patients with cirrhosis develop some degree of hepatic encephalopathy.^{1, 2} Overt hepatic encephalopathy is associated with a poor prognosis, with survival rates of 42% at 1 year and 23% at 3 years.^{2, 3} Treatment options for patients with hepatic encephalopathy continue to improve with increasing research efforts.

For these and many more reasons, an advisory panel (Special Issues Board) of physicians and pharmacists who specialize in the field of liver disease and liver transplantation was convened on December 5, 2009, in Las Vegas, Nevada. This Special Issues Board was supported by an unrestricted educational grant from Salix Pharmaceuticals, Inc., Morrisville, North Carolina. The main purpose of the Special Issues Board meeting was to review published data and facilitate in-depth discussions regarding issues of particular importance to health system pharmacists in the management of hepatic encephalopathy. The meeting provided those in attendance with a balanced educational opportunity geared toward improving pharmacists' understanding of the management of hepatic encephalopathy.

The meeting objectives for accomplishing this goal included presentations of data and follow-up discussions on various aspects of diagnosing and managing hepatic encephalopathy. Three specialists

facilitated this process by discussing practice guidelines, clinical management of the disorder, and treatment options, including rifaximin, a nonabsorbed antibiotic. Compliance with treatment issues and pharmacoconomics were also discussed. In addition, the faculty participated in discussions with an expert panel of pharmacists from across the United States regarding specific issues that pharmacists face at their individual institutions.

The important aspects of each of these presentations and discussions are captured in the articles included in this supplement. The supplement is not intended to provide a thorough review on each topic, but to highlight what is new and cutting edge in the field.

As program Chair, I reviewed the most recent practice guidelines for hepatic encephalopathy, which were published in 2001.¹ Today, these guidelines are causing confusion in many institutions since they are not based on current evidence-based data. In addition, they do not reflect the results of significantly new data that are available regarding treatment interventions and outcomes. In light of newer, well-designed, well-controlled clinical trial data and the U.S. Food and Drug Administration approval on March 24, 2010 for rifaximin for treating overt hepatic encephalopathy, a complete reassessment and reprioritization of treatment approaches is warranted.

Dr. Thomas Schiano presented an overview of clinical management of hepatic encephalopathy. He reported that the pathophysiology of hepatic encephalopathy is extremely complex. The clinical manifestations of the disorder include mental or personality changes, asterixis, decreased energy levels, impaired cognition, impaired sleep-wake cycle, decreased hand-eye coordination, psychomotor retardation, and incessant talking.^{4, 5} The presence of high ammonia levels may be helpful in diagnosing the disorder, but its role is

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largely hypothetical. The West Haven Criteria are the most-often used scoring system to determine hepatic encephalopathy; however, like other scoring systems, it is highly subjective.

Treatment options for hepatic encephalopathy were also presented by Dr. Schiano. These include lactulose, which has been used for many years to minimize the effects of hepatic encephalopathy, and rifaximin, a semisynthetic, nonsystemic antibiotic. Lactulose, which has long been used as first-line therapy in treating hepatic encephalopathy, has demonstrated efficacy over placebo, but has shown no benefit in survival.⁶ Abdominal cramping, diarrhea, and flatulence are commonly seen adverse events, thus impeding long-term compliance and adherence.⁷

A review of placebo-controlled treatment comparisons and open-label studies of the use of rifaximin in the management of hepatic encephalopathy determined that the agent was effective in improving behavioral, laboratory, mental status, and intellectual abnormalities.⁸ Patients who were administered rifaximin required fewer hospitalizations, had shorter lengths of hospital stays, and experienced lower hospital charges compared with lactulose-treated patients. Rifaximin was judged to be at least equally effective as, and in some studies superior to, nonabsorbable disaccharides such as lactulose and lactitol in reducing signs and symptoms in patients with mild-to-moderately severe hepatic encephalopathy.

The issues regarding patient compliance with treatment options, especially in a patient with cirrhosis and hepatic encephalopathy, were discussed by Dr. Guy Neff. Compliance data from a small medical record review study showed that noncompliance with lactulose was predominantly (90%) attributed to gastrointestinal adverse effects.⁹ Another retrospective medical record review showed that adverse effects were less frequently reported and compliance with treatment was greater during rifaximin therapy versus lactulose therapy.¹⁰

According to Dr. Neff, it is well known that the pharmacoeconomic burden of chronic liver disease and hepatic encephalopathy is rising. Most patients with hepatic encephalopathy (71%) were Medicare or Medicaid patients, as reported in a 2002 national statistics report.³ Although the length of hospitalization for patients with hepatic encephalopathy has

decreased from 1993 to 2007, hospitalization costs for the same time period have risen from about \$13,000 to \$30,000, with a larger percentage of patients discharged to nursing homes or rehabilitation facilities, rather than home. Total charges in the United States for hepatic encephalopathy hospitalizations from 1994–2003 were \$5.9 billion, with \$1.3 billion occurring in 2003 alone.³

Dr. Neff also reported on a retrospective review of costs associated with lactulose and rifaximin treatment that he and his colleagues conducted in 2006.¹¹ The total number of hospitalizations and average length of stay were much lower in the rifaximin group. When combining annual drug, hospitalization, and emergency visit costs, they found that rifaximin, although more costly than lactulose on a monthly basis, reduced hospitalization and emergency visit costs and produced a savings of over \$3000/patient/year.

The expert panel of pharmacists from major medical centers across the country engaged in discussions during and after each formal presentation. Many related their frustration with practice guidelines not being applicable to their institutions. All endorsed the recommendation that the current guidelines be updated or that new formal evidence-based guidelines be established. Participants also agreed that noncompliance with treatment is a major issue and that they employ various interventions, including educational materials and group and individual discussions, to highlight the consequences of being compliant or noncompliant with treatments.

Finally, the expert panel of pharmacists discussed anticipated health care reform and stated that many institutions need to change their mode of thinking to examine disease states rather than just costs associated with medicines or different therapies, thereby removing the “silo mentality” that currently exists. They agreed that pharmacists must be able to demonstrate that certain treatments, such as rifaximin, although more costly on a daily basis, actually reduce an institution’s overall health care costs.

The collective research on diagnosing and treating patients with hepatic encephalopathy, which is provided in the articles and discussions in this supplement, should assist practicing pharmacists in disseminating relevant information about hepatic encephalopathy to other health care providers and patients and in making important formulary decisions about treatments.

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