

Pharmacoeconomics of Hepatic Encephalopathy

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Understanding and appreciating the science of pharmacoeconomics have become even more important for health care providers and insurers during the recent economic downturn. Evaluating the true costs of any disease is complex; both direct costs, such as costs of drug therapy and the provision of care, and indirect costs, such as lost earnings and reduced quality of life, must be taken into account. With chronic liver disease, the most recent data indicate that direct costs were more than \$2 billion whereas indirect costs were more than \$450 million. Hepatic encephalopathy, a common complication of chronic liver disease, contributes to this economic burden. Although patients' length of stay during hospitalization for hepatic encephalopathy decreased from almost 9 days to 6 days (and has remained stable over the past few years) from 1993 to 2007, hospitalization costs rose from \$13,000 to \$30,000/hospital stay. In addition, 22% of patients were discharged directly to nursing homes or rehabilitation centers, which increases total costs. When assessing therapy for hepatic encephalopathy, it is important to consider the total costs of the disease, not just treatment costs. Although more expensive on a daily basis than lactulose, rifaximin has been shown to reduce hospitalization rates, has a better adverse-effect profile, and increases patient compliance. One study found that rifaximin produced a cost savings/patient/year of more than \$3000 over lactulose therapy.

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Health care providers and insurers should understand and appreciate the issues surrounding pharmacoeconomics, especially during times of economic decline. In fact, the continued worldwide economic downturn will challenge the ability of clinicians to appropriately manage diseases and yet remain cognizant of the costs of treatment. Evaluating the total costs of any

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disease is complex; both direct medical costs (e.g., costs associated with drug development, drug acquisition, hospitalization, and physician office and emergency department visits) and indirect costs (e.g., lost earnings, pain and suffering, and the value of care by family members) must be considered. Health care cost analysis models can approximate patients' quality-adjusted life-years, measuring total costs over time, and provide multiple-year cost calculations. However, the medical community has struggled with calculating health care expenditures precisely and, more important, providing that information to the health care provider.

The costs associated with chronic liver disease are high and continue to increase. Hepatic encephalopathy, a common complication of liver disease, has its own set of costs. The objective of this article is to provide pharmacists with a

concise overview of the pharmacoeconomic issues concerning hepatic encephalopathy.

Cirrhosis and Hepatic Encephalopathy

Most patients with cirrhosis develop some degree of hepatic encephalopathy. Up to 80% of patients with cirrhosis develop minimal hepatic encephalopathy (MHE; defined as subclinical or latent)¹; 30–45% of patients with cirrhosis and 10–50% of those with a transjugular intrahepatic portosystemic shunt develop overt hepatic encephalopathy.² The true incidence and prevalence of hepatic encephalopathy are difficult to establish. Because patients experience few symptoms with MHE, the disease is often not recognized until hepatic encephalopathy progresses to more severe disease. Even with overt hepatic encephalopathy, diagnosis may be delayed or missed due to considerable differences in the disease's etiology and spectrum of severity.³ What is known is that the prognosis after developing overt hepatic encephalopathy is poor, with 1- and 3-year survival rates of 42% and 23%, respectively.⁴

Unfortunately, most physicians do not routinely test for MHE. In a survey conducted by the American Association of Liver Disease, 84% of the 137 respondents recognized that MHE is a significant problem, and 74% stated that they should test for MHE.⁵ However, 38% of respondents reported that they never test for the disorder, 34% test for MHE less than 50% of the time, 14% test 50–80% of the time, and only 14% reported that they test more than 80% of the time. Few respondents test for MHE in every patient with cirrhosis.

Economic Burden of Chronic Liver Disease

The many factors that constitute the costs of managing a disease vary depending on the disease and its severity. When determining the total cost of a disease, certain factors must always be included: drug costs, which include costs of research and development, marketing, and manufacturing; disease costs, which take into account the costs of morbidity and mortality; and the prevalence of the disease. Direct costs must then be combined with the indirect costs of the disease. Indirect costs include quality of life (e.g., employment status, ability to function independently, and family relationships) plus cost of treatment cure.

The direct costs of chronic liver disease were reported to be over \$2 billion and are rising.⁶

Table 1. Direct Costs of Chronic Liver Disease

Type of Care	Cost (\$)
Inpatient hospitalizations	1,403,400,000
Outpatient hospital visits	\$67,600,000
Emergency room visits	\$7,000,000
Physician office visits	\$88,700,000

From reference 6, using data from the 1995 National Health Interview Survey, adjusted to 1998 values.

This figure includes costs of inpatient hospitalization, outpatient hospital visits, emergency department visits, and physician office visits (Table 1). Based on 2004 data, the costs of drug therapy alone to treat chronic liver disease were more than \$1 billion⁶; these costs are also rising. The indirect cost of lost wages due to hospitalization was over \$225 million.⁶ When additional lost wages related to time spent at physician office visits, emergency department visits, and outpatient visits were included, the total adjusted cost of lost wages was more than \$272 million.⁶

Overall costs of chronic liver disease are also increasing because of a higher reported occurrence of the disease and related severity. A study of the disease burden of hepatocellular carcinoma between 1998 and 2008 reported a 68% increase in the incidence of hepatocellular carcinoma and a 61% increase in the number of patients diagnosed with cirrhosis.⁷ It also reported a 528% increase in the need for liver transplantation, a 279% increase in decompensation, and a 223% increase in liver-related deaths.

The United States health care system is truly being affected by these increasing costs. According to national statistics reported in 2002, 71% of patients with hepatic encephalopathy (identified by using all relevant *International Classification of Diseases, Ninth Revision, Clinical Modification* codes) had Medicare or Medicaid insurance.⁸ Only 22% had private insurance, and 7% were coded as uninsured or other. In addition, 59% of patients diagnosed with cirrhosis were insured by Medicare or Medicaid, 25% had private insurance, and 16% were coded as being uninsured or other.

Between 1993 and 2007, the length of hospital stay for patients with hepatic encephalopathy decreased from almost 9 days to 6 days (and has remained stable over the past few years), but costs of hospitalization rose from approximately \$13,000 to \$30,000/hospital stay.⁸ Although patients with hepatic encephalopathy are spending fewer days in the hospital, the percentage of

patients being discharged to nursing homes or rehabilitation centers increased from 2.6% to 22.1%.⁹

The total cost of hospitalization for hepatic encephalopathy in U.S. hospitals from 1994–2003 was \$5.9 billion, with \$1.3 billion of those costs occurring in 2003 alone.⁸ The total hospital cost for cirrhosis during the same time period was a staggering \$19.6 billion. These costs are expected to escalate.

Pharmacoeconomics of Hepatic Encephalopathy Treatments

Several economic reviews of hepatic encephalopathy treatment have been published. In one small retrospective study, the medical records of 39 patients who had undergone liver transplantation and had hepatic encephalopathy (West Haven criteria grade 2) were reviewed.⁹ Twenty-four patients received lactulose 60 g/day and 15 received rifaximin 1200 mg/day. Total number of hospitalizations and average lengths of stay were lower in the rifaximin group (Table 2). When annual drug costs plus the costs associated with hospitalizations and emergency department visits were analyzed (Table 3), rifaximin, although more costly on a monthly basis, reduced hospitalization and emergency department visit costs and actually produced a mean cost savings/patient/year of \$3327. The total annual cost savings extrapolated for all 39 patients would be almost \$170,000. These data did not include indirect costs such as those pertaining to physician office visits, phone calls, drug compliance, and other potential medical expenditures. Further analysis is ongoing.

Other researchers compared the frequency of hospitalizations and related outcomes during treatment of hepatic encephalopathy with lactulose versus rifaximin.¹⁰ Patients were initially treated with lactulose; after 6 months, they were switched to rifaximin for an additional 6 months. Results showed that the frequency and duration of hospitalization were 3 times lower when patients were receiving rifaximin versus lactulose. Total length of hospital stays and total charges/patient/hospital stay were 4 times lower during rifaximin treatment versus lactulose treatment. These results may be attributed to less severe illness after receiving the lactulose therapy before rifaximin; this is supported by findings of lower hepatic encephalopathy grade and less frequent asterix when the patients were receiving rifaximin.

To calculate the cost effectiveness of six different

Table 2. Number of Hospitalizations and Length of Stay in Patients Receiving Lactulose versus Rifaximin⁹

Study Outcome	Lactulose Group (n=24)	Rifaximin Group (n=15)
Total no. of hospitalizations	19	3
No. of Patients		
No. of hospitalizations		
1	2	3
2	4	0
3	3	0
Mean (range)		
Length of stay (days) ^a	5.0 (3–10)	3.5 (3–4)

^aDifference between groups was significant ($p < 0.0001$).

treatment strategies for hepatic encephalopathy, researchers performed a decision analysis.¹¹ The six strategies were as follows: no treatment, lactulose monotherapy, lactitol monotherapy, neomycin monotherapy, rifaximin monotherapy, and lactulose with crossover to rifaximin if the patient had poor response or intolerance to lactulose (rifaximin salvage). The primary outcome was cost/quality-adjusted life-year gained. Under base case conditions, the researchers found that no treatment was least expensive and rifaximin salvage was most expensive. They also found that although rifaximin monotherapy was the most expensive monotherapy approach, it also was the most effective treatment for hepatic encephalopathy. Rifaximin salvage therapy was most effective in patients who demonstrated a poor response or intolerance to lactulose. Rifaximin salvage prevented overt events, and the researchers deemed the salvage approach a cost-effective strategy.

Another retrospective study found that the risk of hospitalization, as well as the number and duration of hospitalizations, were lower in patients receiving rifaximin monotherapy compared with those receiving lactulose followed by rifaximin, or lactulose monotherapy.¹² Fewer patients experienced spontaneous bacterial peritonitis while taking rifaximin compared with the lactulose treatment groups, and fewer adverse events were reported in patients receiving rifaximin versus those who had been treated with both drugs.

In a recently subanalysis of data from a phase III, placebo-controlled trial, rifaximin 1100 mg/day provided significant protection against hepatic encephalopathy–related hospitalizations compared with placebo (48% risk reduction) during a 6-month treatment period.¹³ According to the authors, the number needed to treat was nine to

Table 3. Overall Cost Savings with Rifaximin versus Lactulose Therapy⁹

Treatment Group	Mean Drug Cost/ Patient/Month	Mean Total Treatment Cost/Patient/Year ^a	Total Treatment Cost/Year
Lactulose (n=24)	\$50	\$13,285	\$318,839 ^b
Rifaximin (n=15)	\$662	\$9958	\$149,372 ^b
Difference	\$612 (\$7344/yr)	\$3327	\$169,467 total savings

^aIncludes annual drug costs plus costs of hospitalizations and emergency department visits for 19 hospitalizations (in 9 patients) in the lactulose group and 3 hospitalizations (in 3 patients) in the rifaximin group.

^bCost extrapolated for all 24 patients in lactulose group and all 15 patients in the rifaximin group.

prevent one episode of hepatic encephalopathy-related hospitalization.

Conclusion

The economic burden of hepatic encephalopathy and advanced liver disease is enormous and is expected to worsen. As hepatic encephalopathy is often not diagnosed, its reported prevalence is most likely underestimated. Nonetheless, annual admission rates for the disease have increased over the past 10 years, and this trend is expected to continue. The true measure of the expense of hepatic encephalopathy is the overall cost of hospitalization. In addition to increased admissions, the actual cost of each hospitalization has increased, and more patients are being discharged to nursing homes or rehabilitation facilities, which translates to higher costs.

Preventing hospitalizations in patients with cirrhosis suffering from hepatic encephalopathy is key to economic success. Standard diagnostic criteria and routine testing for MHE are needed so that a patient can be treated before the disease progresses to cerebral dysfunction, which can decrease a patient's overall quality of life. Therapy that can reduce the number of hospitalizations as well as length of stay will help improve patients' quality of life and be economically advantageous. Rifaximin is a promising drug for hepatic encephalopathy, and further economic analyses with this treatment and others should be performed. Understanding the entire cost-benefit profile of a drug is important when treating patients with hepatic encephalopathy.

Participants' Discussion

After the live presentation that was the basis for this article, pharmacists participated in a panel discussion.

1. How do you see pharmacoeconomic information fitting into your drug decision-

making strategies?

Several pharmacists stated that the medical community must change its mode of thinking. Clinicians and insurers need to look at the cost of the disease rather than just the cost of therapy, thereby removing what is called the "silo mentality." One participant acknowledged that it is difficult to attribute reduced hospital length of stay specifically to one agent or treatment. Others pointed out that integrated health networks, such as Kaiser Permanente and the Veterans Administration, take into account total costs of care (inpatient, outpatient, and treatment) rather than just the cost of one aspect of care. They have, in effect, replaced the silo mentality with a whole disease state mentality in their decision-making. Others in attendance stated that most medical centers have too many different silos. The directors of each department are often judged on how they manage their own budgets, rather than examining the issues of cost and utilization of services globally.

2. Do you look at issues on a global or departmental basis?

During the next 10 years, pharmacists will be involved much more in global decision-making strategies. Currently, they evaluate drug selection concurrently with issues of safety, costs, and efficacy. They need to be able to justify to upper management that a higher treatment cost may be able to keep patients out of the hospital and save the facility thousands of dollars/year. Richard Thompson, Pharm.D., program chair, stated that at all institutions, there is an administrator whose primary role is the overall financial stability of the institution. An advocate who understands these issues can work through the channels up to that level. One participant stated that the clinicians who serve on a hospital's pharmacy and therapeutics committee should be educating corporate

administrators about cost-saving information. These administrators can then make an evidence-based recommendation, which can affect decisions for the pharmacy departments.

Another participant commented that the entire incentive reimbursement program is flawed because it doesn't allow clinicians to use the most effective therapy. The idea of salvage therapy is one way for pharmacists to defend reimbursement for rifaximin. Most insurance companies cover the cost of rifaximin for treating overt hepatic encephalopathy, which received approval in March 2010 by the U.S. food and Drug Administration.

3. Do high drug copayment plans affect prescribing decisions at your institution?

Several participants expressed concern about patients who are or will be enrolled in Medicare or Medicaid with Part D drug plans. Many individuals choose a Part D program that provides a low monthly premium cost but requires high prescription copayments. For patients who take three or four prescription drugs each day, a higher monthly premium combined with a low prescription copayment may make more economic sense. In addition, insurance plans often require some drugs, such as rifaximin, to receive prior authorization before reimbursement can occur. Ultimately, selecting the correct plan is a matter of educating patients.

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References

1. Bajaj JS. Management options for minimal hepatic encephalopathy. *Expert Rev Gastroenterol Hepatol* 2008;2:785–90.
2. Poordad FF. Review article: the burden of hepatic encephalopathy. *Aliment Pharmacol Ther* 2007;25(suppl 1):3–9.
3. Lewis M, Howdle PD. The neurology of liver failure. *QJM* 2003;96:623–33.
4. Bustamante J, Rimola A, Ventura PJ, et al. Prognostic significance of hepatic encephalopathy in patients with cirrhosis. *J Hepatol* 1999;30:890–5.
5. Bajaj JS, Etemadian A, Hafeezullah M, Saecian K. Testing for minimal hepatic encephalopathy in the United States. *Hepatology* 2007;45:833–4.
6. American Gastroenterological Association. The burden of gastrointestinal diseases, 2001. Available from www.gastro.org/clinicalRes/burdenReport.html. Accessed December 3, 2009.
7. Davis GL, Albright JE, Cook S, et al. Projecting the future healthcare burden from hepatitis C in the United States. *Hepatology* 1998;28(suppl 4 pt 2):390A.
8. Agency for Healthcare Research and Quality. HCUPnet, healthcare cost and utilization project. Available from www.hcupnet.ahrq.gov. Accessed May 14, 2009.
9. Neff GW, Kemmer N, Zacharias VC, et al. Analysis of hospitalizations comparing rifaximin versus lactulose in the management of hepatic encephalopathy. *Transplant Proc* 2006;38:3552–5.
10. Leevy CB, Phillips JA. Hospitalizations during the use of rifaximin versus lactulose for the treatment of hepatic encephalopathy. *Dig Dis Sci* 2007;51:737–41.
11. Huang E, Esrailian E, Speigel BM. The cost-effectiveness and budget impact of competing therapies in hepatic encephalopathy—a decision analysis. *Aliment Pharmacol Ther* 2007;26:1147–61.
12. Mantry PS, Munsaf S. Analysis of the effect of rifaximin plus lactulose on hospitalizations in patients with end-stage liver disease. Poster presented at the 59th annual meeting of the American Association for the Study of Liver Diseases, San Francisco, CA, October 31–November 4, 2008.
13. Neff G, Leevy C, Frederick T, et al. Rifaximin reduces the risk of hospitalizations in patients with previous episodes of hepatic encephalopathy: results from a phase 3 placebo-controlled trial. Presented at digestive disease week, Chicago, IL, May 31, 2009.