

Factors Affecting Compliance and Persistence with Treatment for Hepatic Encephalopathy

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Noncompliance with treatment protocols produces an increased burden on the health care system. Reports show that 23% of annual admissions to nursing homes in the United States (380,000 patients) are due to noncompliance, resulting in overall costs of over \$31 billion. More than 10% of all patients (3.5 million) are hospitalized each year due to complications related to noncompliance, with over \$15 billion spent. In addition, nearly half of the 2 billion prescriptions filled each year are not taken correctly. Patients with cirrhosis and hepatic encephalopathy who are prescribed lactulose experience a greater frequency of adverse effects, require more hospitalizations, and suffer more disease recurrence than those prescribed rifaximin.

Key Words: cirrhosis, compliance, hepatic encephalopathy, medical adherence, negative economic effects, noncompliance, prescriptions.
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The definition of medical compliance is following medical advice correctly. Former United States Surgeon General C. Everett Koop, M.D., summarized the situation quite succinctly when he stated, “Drugs don’t work in patients who don’t take them.” Therapeutic compliance, however, is very difficult to quantify for any disease entity. Patients suffering from cirrhosis are often noncompliant with their treatment, thus comorbidity issues related to the varying degrees of hepatic encephalopathy, a common complication of cirrhosis, are a concern.^{1,2} Overt hepatic encephalopathy is associated with poor prognosis, with survival rates of 42% at 1 year and 23% at 3 years.³ This article presents an

overview of various compliance issues that can affect clinical outcomes in patients with cirrhosis and hepatic encephalopathy.

Compliance versus Adherence

Many health care providers assume that compliance and adherence are synonymous, but there are subtle differences between the two terms. General medical compliance revolves around the degree of consistency and accuracy with which a patient follows a prescribed regimen, as distinguished from adherence, which involves maintenance of treatment plans. Adherence is defined as the extent to which patients take their drugs as prescribed (i.e., number of doses taken, timing of doses, and proper administration of doses).⁴ Compliance suggests that patients follow instructions passively rather than being an active participant in the desired treatment plan.

Major predictors of poor adherence to drug therapy include asymptomatic diseases that require treatment, psychological problems (especially depression), patient’s lack of belief in a treatment’s benefit, complex treatments, and adverse effects of treatments. Other factors affecting adherence include a poor provider-

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patient relationship, inadequate follow-up or discharge planning, missed appointments, and drug costs or copayments.⁴ Measuring adherence can be as challenging as measuring compliance but can be evaluated by direct or indirect methods (Table 1).⁴ Patients with cirrhosis, in particular, often have associated complications, such as endocrine problems, daily health concerns, and other issues that may affect compliance or adherence (Table 2).⁵

Compliance

Very simply, compliance means taking the correct amount of the prescribed drug at the proper time. In general, noncompliance with treatment plans causes an increased burden in the use of health care facilities while drastically raising economic expenditures.⁶⁻¹⁰ For example, 23% (380,000 patients) of yearly admissions to nursing homes are due to noncompliance with prescribed treatments, resulting in an overall cost of \$31.3 billion.⁶ Ten percent (3.5 million) of all patients are hospitalized each year due to complications related to noncompliance with treatment strategies, costing over \$15.2 billion.^{7,8}

Approximately half of the 2 billion prescriptions filled each year are not taken correctly.⁹ In another report that assessed compliance, it was found that one third of patients take all their drugs, one third of patients take some of their drugs, and one third of patients do not even fill their prescriptions.¹⁰ Efforts have been proposed to reduce prescription problems. One such idea, decreasing the number of daily doses, has improved compliance.

Although it can be argued that medication errors are not precisely a compliance issue, the

Table 1. Direct and Indirect Methods of Measuring Adherence

Type	Methods
Direct	Observing therapy
	Measuring blood levels of drug or metabolite
	Measuring biologic marker in the blood
Indirect	Using patient questionnaires
	Counting pills
	Monitoring prescription refill rates
	Assessing patient's clinical response
	Using electronic drug therapy monitors
	Measuring physiologic markers
	Monitoring patient diaries
Using questionnaires for caregiver or teacher	

Adapted from reference 4.

importance of them must be noted. Medication errors (prescription writing errors, faults due to erroneous medical decisions, or prescription fulfillment errors) can result in harm to patients. The complexity of the procedures in place throughout the entire prescribing process, especially in a busy medical center, could be reduced by the introduction of automated systems or uniform prescribing charts. Feedback control systems and immediate review of prescriptions, performed by a hospital pharmacist, can reduce the number of errors. In addition, audits should be periodically performed.¹¹

Compliance Issues Specific to Patients with Cirrhosis and Hepatic Encephalopathy

The major reasons that patients with cirrhosis and hepatic encephalopathy become noncompliant can be linked to fatigue and confusion. Another common concern is the frequency with which patients with cirrhosis present to clinic appoint-

Table 2. Issues Affecting Compliance in Patients with Cirrhosis

Category	Examples	Compliance Issues ^a
Endocrine	Diabetes mellitus	Complicated medical regimen, dietary restrictions
Daily health	Quality of life	Decreased energy level from inactivity and muscle wasting Lactulose therapy requires close monitoring and complicates quality of life due to a variety of drug-related adverse effects (e.g., incontinence, abdominal pain, nausea, vomiting, encopresis, marked flatulence, bloating)
	Diet, nutrition	Decreased appetite due to bloating and abdominal pain associated with lactulose use; may also be seen with ascites
Other	Renal insufficiency	Hospitalization, more intensive medical care
	Pulmonary problems	Hospitalization, more intensive medical care
	Fatigue	Hospitalization, more intensive medical care

^aAuthor's observations based on clinical experience.

Adapted from reference 5.

Table 3. Adverse Effects of Rifaximin versus Lactulose

Adverse Effect	No. (%) of Patients ^a		p Value ^b
	Rifaximin Group (n=145)	Lactulose Group (n=145)	
Diarrhea	10 (7)	133 (92)	<0.001
Flatulence	4 (3)	108 (74)	<0.001
Abdominal pain	20 (14)	90 (62)	<0.001
Headache	19 (13)	25 (17)	0.718

^aAdverse effects were monitored in the 145 patients during the last 6 months of lactulose therapy and the first 6 months after switching to rifaximin.

^bUsing the Bowker test for symmetry for maximum severity of side effect.

Adapted from reference 14.

ments without family or caregiver support. Thus, fatigue, confusion, and lack of social support complicate the overall health care management of patients with cirrhosis.

Fatigue is common and potentially profound in patients with chronic liver disease, including biliary cirrhosis and chronic hepatitis C.¹² Fatigue produces a state of increased discomfort, lower capacity for work, and decreased efficiency in accomplishments, usually accompanied by weariness, sleepiness, and irritability. Fatigue often occurs early in treatment and tends to persist, is frequently unresponsive to rest, and is difficult to treat. Most patients with profound fatigue will have problems understanding drug regimens and adhering to them in the long term, especially if the fatigue is accompanied by mental confusion, which is often the case. Limited success has been reported with ondansetron, a serotonin 5-HT₃ receptor subtype antagonist, in alleviating fatigue in some patients with chronic liver disease.¹²

Another common problem in patients with cirrhosis is the lack of family or caregiver support, as many patients come to office visits alone. These patients have no support person who can take part in discussions about a very complicated disease, ask questions that the patient may be unable to articulate, write down detailed drug therapy schedules, or ensure that the patient takes the drugs as prescribed. In addition, a high percentage of patients with cirrhosis and hepatic encephalopathy have decreased short-term memory and lose the ability to fully understand instructions, let alone remember them.

A simplified dosage regimen maximizes adherence to treatment. Data from a systematic review of 76 trials that employed electronic monitors to assess adherence or compliance found that increased frequency of dosing

adversely affected adherence levels.⁴ Once-daily dosing regimens were associated with an approximately 80% adherence rate, whereas 4 times/day dosing regimens achieved adherence rates of only approximately 50%. Clearly, the more simplified the dosing schedule, the greater the rate of adherence or compliance.

Compliance Data from Hepatic Encephalopathy Trials

Several recent medical record reviews and clinical trials of patients with hepatic encephalopathy have examined compliance with the medical regimen as part of the overall trial protocol. In one retrospective medical record review, 119 patients taking lactulose for cirrhosis were evaluated for hepatic encephalopathy in a liver transplant center.¹³ Eighty-three patients experienced recurrence; in 33 (40%) of them, it was due to noncompliance with lactulose. Their noncompliance was predominantly (90%) due to gastrointestinal adverse effects. Ten percent of patients were unwilling to be treated with lactulose. A significantly higher rate of further hospitalization for hepatic encephalopathy occurred with either lactulose overuse or noncompliance when recurrence of precipitating factors was assessed. The authors noted that alternative drugs that minimize gastrointestinal adverse effects may increase compliance rates in this patient population. No significant difference in duration of time until death or liver transplantation was noted between the compliant and noncompliant groups (p=0.09).

Another retrospective medical record review of 145 patients with hepatic encephalopathy compared patient-reported 1-year compliance rates for two treatment regimens: the last 6 months of lactulose treatment versus the first 6

months after switching to rifaximin 1200 mg/day.¹⁴ The frequency and duration of hospitalization were 3 times lower for the rifaximin group than the lactulose group due to a decrease in overt hepatic encephalopathy events in the rifaximin group. Total length of hospital stay and total costs/patient/hospital stay were 4 times lower in the rifaximin group than in the lactulose group. The authors postulated that these results might be attributed to less severe illness in patients during rifaximin therapy, a possibility that was supported by the findings of lower grade hepatic encephalopathy and less frequent asterixis with rifaximin. In addition, adverse effects were less frequently reported (Table 3), and compliance with treatment was greater (Table 4) during rifaximin therapy. Although better compliance with a rifaximin regimen may contribute to better clinical and economic outcomes, these results should be interpreted cautiously because the order of treatments was not counterbalanced (i.e., there was no group that started rifaximin, then switched to lactulose therapy).

A phase III study of rifaximin versus placebo was undertaken to evaluate the maintenance of hepatic encephalopathy remission.¹⁵ This study also carefully examined compliance issues. Patients in hepatic encephalopathy remission were treated with either rifaximin 1100 mg/day (140 patients) or placebo (159 patients) for up to 6 months. During the study, 91% of the patients in both study groups continued lactulose treatment. Compliance with treatment was based on pill counts (numbers of tablets dispensed by and returned to the pharmacist). Patients were considered to be compliant with therapy if they took 80–120% of the expected number of tablets. Eighty-four percent of patients who received rifaximin and 85% of patients who received placebo were deemed compliant. Safety data from the phase III study showed that rifaximin had a safety profile similar to placebo.¹⁶

Clinical Trials of Cirrhosis and Long-Term Gastrointestinal Bleeding

A long-term (1-yr), randomized, placebo-controlled efficacy study of nadolol to prevent initial gastrointestinal bleeding in patients with cirrhosis had a compliance component.¹⁷ The study design defined noncompliance as a patient not taking study drug for 2 or more consecutive days, as reported to investigators by the patient or a family member. Thirteen (25%) of 53

Table 4. Self-Reported Compliance with Rifaximin versus Lactulose

Percentage of Doses Taken	No. (%) of Patients ^{a, b}	
	Rifaximin Group (n=145)	Lactulose Group (n=145)
0–24%	0 (0)	5 (3)
25–49%	1 (< 1)	21 (14)
50–74%	6 (4)	74 (51)
75–99%	76 (52)	37 (26)
100%	58 (40)	7 (5)

Differences between groups were significant ($p < 0.001$ for all comparisons, Bowker's test for symmetry).

^aData were missing for four patients in the rifaximin group and one patient in the lactulose group.

^bCompliance was measured in the 145 patients during the last 6 months of lactulose therapy and the first 6 months after switching to rifaximin.

Adapted from reference 14.

patients who were given nadolol prophylactically were noncompliant versus 6 (11%) of 53 who received placebo. According to the authors, nadolol reduced the risk of bleeding in those patients who were compliant.

Compliance was also a significant factor in preventing recurrent gastrointestinal bleeding in patients taking propranolol. A long-term prospective study of 127 patients with cirrhosis who were hospitalized for gastrointestinal bleeding from ruptured esophageal varices or acute gastric erosion requiring blood transfusions were administered propranolol 120 mg/day (median dose; range 20–480 mg/day during follow-up) for 1–3 years.¹⁸ Compliance was defined as never stopping drug therapy or never forgetting to take propranolol twice/day. After 2 years, 64% of patients were free of rebleeding. A total of 78 patients (61%) were compliant at 2 years. Noncompliance with treatment was associated with risk for rebleeding ($p = 0.02$).

Conclusion

Compliance with treatment regimens can affect clinical outcomes in patients with cirrhosis and especially in patients suffering from hepatic encephalopathy. Compliance rates with rifaximin are at least as good as or better than those seen with placebo or lactulose in patients with hepatic encephalopathy. Most important, however, is that because the frequency of adverse effects is lower than lactulose and the rifaximin dosage remains constant on a daily basis, compliance with rifaximin therapy is greater than with lactulose, resulting in decreased hospitalizations and recurrences of hepatic encephalopathy.

Participants' Discussion

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

1. Are compliance issues addressed at your institution through patient education or other methods?

One pharmacist stated that New York started an initiative with health care workers focusing on diabetes mellitus to improve compliance. With once-daily dosing schedules, compliance is at about 90%, whereas with twice- or thrice-daily dosing, the rate drops dramatically (45–50%). Some techniques tried include preparing handouts for patients, seeing them at subsequent visits, having patients explain exactly what they are doing, and probing on the issues that they face when not complying with treatment regimens. With hepatic encephalopathy and its associated short-term memory loss problems, the task is more difficult.

Another pharmacist reported that in pre-liver transplantation programs, a lot of time is spent in group and individual settings with patients and family members discussing the process and consequences of being compliant or noncompliant with treatments. Noncompliance is a risk management issue in his institution, and they constantly struggle with compliance issues in the pretransplant setting. He acknowledged that they use compliance as a tool to assess what type of patient (compliant or noncompliant) an individual is going to be after transplantation. He added that another issue that relates to compliance or adherence is the ability of patients or insurance providers to cover drug costs. When patients lose their insurance, suddenly they may begin to adjust their drug dosages downward to extend drug availability. Prescribers need to know that the ability to pay for drugs greatly impacts the adherence-to-drug regimen compliance issue.

Dr. Neff pointed out that in some facilities, if patients awaiting kidney transplantation miss several consecutive days of dialysis, they may be removed from the renal transplant list.

Dr. Schiano stated that family involvement is very important. A physician extender (i.e., a nurse practitioner or physician assistant) is able to spend more time talking with the patient and family and providing more follow-

up than a busy clinician who sees 30–60 patients. In the transplantation offices at Mount Sinai Medical Center, these coordinators do the yeoman's work of trying to educate the patient about disease and compliance issues. Another pharmacist reported having a nurse practitioner liver transplant coordinator and one Pharm.D. in the liver clinic. No formalized system for monitoring adherence or providing education regarding advanced liver disease exists at his institution.

Dr. Neff brought up the fact that full-time-equivalent workers and relative value unit measurements are being utilized at many hospitals at a much higher level due to the excessive one-on-one teaching required for these patients. This time spent teaching by the health care provider is nonreimbursable and contributes to clinic or department overhead. The future will require health care providers to find less time-consuming procedures and therapies for the management of cirrhosis.

Dr. Thompson said that although many patients receive an educational component with their initial diagnosis and prescription, a great need exists for continuous reeducation, reinforcement, and reminders of the importance and need for compliance. The question is how the costs associated with this activity are going to be covered since all of these measures are unfunded, time consuming, and without reimbursement.

One participant stated that the pharmacists at his institution spend 10–20 minutes with patients with hepatic encephalopathy at discharge. Dosing for lactulose ranges from 2–4 times/day. The dosing frequency can be reduced if diarrhea develops or increased if the patient has less than two or three soft stool movements/day. Most participants stated that their institutions basically provide discharge education for patients with hepatic encephalopathy, emphasizing the importance of treatment compliance. Others in the pretransplant stage attend group classes. Once patients are listed for transplantation they are given individualized education in the clinic. After transplantation, family education continues.

2. Can you accurately define the demographics of your patients with hepatic encephalopathy?

Several pharmacists agreed that hepatic encephalopathy is a complicated and challenging disease, and the demographics of

patients with hepatic encephalopathy vary widely. Patient types include workers and nonworkers, those involved and not involved with their disease, those with high and low IQ levels, and those who have family or no family support. A substantial amount of time must be spent with a patient with cirrhosis and hepatic encephalopathy who does not have family involvement. Often, these patients come to the emergency department and are admitted to the hospital for a 5- or 6-day stay costing more than \$30,000. One participant stated that some patients with higher IQ levels rationalize their noncompliance with drugs. One would expect them to be the patients who know the benefits of compliance, but they simply talk themselves out of taking their drugs as prescribed, for any number of reasons.

3. Do you see a decline in providers managing patients with liver disease?

According to Dr. Neff, it is important to note that the percentage of health care providers willing to manage patients with liver disease is decreasing. Furthermore, the complicated patient with cirrhosis requires more time involving teaching and problem-related issues. Reimbursement is lacking for the time and effort spent with the patient who has cirrhosis and hepatic encephalopathy and who is receiving a drug that requires daily adjustments according to bowel habit results. For that reason, rifaximin is a promising therapy for improving compliance in the hepatic encephalopathy patient population.

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