

Hepatic Encephalopathy Update: Prophylactic Therapy to Prevent Hepatic Encephalopathy



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Objectives:

- Recognize that elements of neurocognitive impairment associated with overt hepatic encephalopathy may be irreversible and cumulative, thus warranting prophylactic therapy in cirrhotic patients at risk for developing this complication of advanced liver disease
- Identify computerized tests for neurocognitive function that are appropriate for use in community-based clinical practice for diagnosing covert hepatic encephalopathy
- Assess the efficacy and tolerability of lactulose and rifaximin as primary and secondary prophylactic agents for preventing overt hepatic encephalopathy

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Hepatic encephalopathy (HE) is a complication of cirrhosis of the liver characterized by neuropsychiatric abnormalities. The neuropsychiatric abnormalities range from cognitive deficits (referred to as subclinical HE, minimal HE [MHE], or more recently, covert HE [CHE]), which can only be diagnosed by specialized testing to clinically apparent neuropsychiatric complications consisting of alterations in consciousness and motor disturbances (referred to as overt HE [OHE]).^{1,2} An estimated 60% to 80% of patients with advanced liver disease have evidence of cognitive dysfunction or CHE, while 30% to 45% of patients with cirrhosis develop OHE. The annual risk of developing OHE in cirrhotic patients is 20%.³ An estimated one-third to one-half of hospitalizations for cirrhosis are related to OHE, and the frequency of hospitalization for OHE has nearly doubled over the last decade. Average hospital lengths of stay for OHE range between 5 and 7 days. CHE affects a patient's employability, fitness for driving, and self-care.⁴

While it was previously thought that those who recovered from an episode of OHE had no residual neurocognitive impairment, this notion has been challenged. Recent studies have found persistent and cumulative deficits in working memory and learning in cirrhotic patients evaluated before and after the onset of OHE when compared with results of repeat cognitive testing in patients who remained free of OHE.⁵ A study that compared cognitive function in patients who had suffered from OHE prior to liver transplantation with that of a similar group of patients without OHE found neurocognitive abnormalities in the OHE pre-liver transplant group but not in the no-OHE pre-liver transplant group when compared with normative data. Testing was done approximately 1.5 years following liver transplant.⁶ These findings suggest that episodes of OHE may lead to neurologic injury that is not reversible and may have important implications in assigning priority for liver transplantation.⁵ More aggressive prophylactic therapy to prevent OHE episodes may also be warranted in those awaiting transplant. Sharma et al have proposed using the terms primary prophylaxis for therapy administered to cirrhotic patients to prevent development of a first episode of OHE and secondary prophylaxis for therapy administered to prevent recurrence of OHE in patients who have already experienced an episode of OHE.⁷ This newsletter will focus on recent research that adds insight to the use of prophylactic therapy—both as primary prophylaxis and as secondary prophylaxis—to prevent OHE including selected data presented at Digestive Disease Week 2012 (DDW 2012). DDW 2012 was held from May 19 to May 22 in San Diego, California.

Primary prophylactic therapy for prevention of OHE in cirrhotic patients who have never experienced an OHE episode

As mentioned above, 30% to 45% of patients with cirrhosis will develop OHE, and the annual risk for OHE is 20% for patients with cirrhosis. Sixty percent to 80% of cirrhotic patients will develop CHE.³ Several recent studies document the effectiveness of prophylactic therapy in cirrhotic patients prior to the first occurrence of an OHE episode. Agrawal et al compared the effects of treatment with lactulose versus no treatment in cirrhotic patients who had never experienced an episode of OHE. Patients were followed monthly for a median of 12 months. During the follow-up, 6 of 55 patients (11%) who received lactulose versus 15 of 50 patients (30%) in the untreated group developed an episode of OHE. Of patients who were diagnosed with CHE in the lactulose-treated group, 66% showed improvement during treatment. The authors concluded that lactulose was effective for the prevention of OHE in patients with no prior history of OHE and also improved cognitive function in those with CHE.⁸

Rifaximin has also been studied in cirrhotic patients without current or past history of OHE. All patients included in the study had a diagnosis of CHE. Patients received either rifaximin (n = 49) or placebo (n = 45) for 8 weeks. Following 8 weeks of therapy, 75.5% of the patients receiving rifaximin had a reversal of CHE compared with 20% of the patients receiving placebo. Rifaximin therapy resulted in a significant reduction in 7 of 12 scales of the Sickness Impact Profile (SIP) score, the total psychosocial and physical subscores, and the total SIP score after 8 weeks of treatment indicating an improvement in health-related quality of life. None of the changes in SIP scores in the placebo group were significant. While the study duration was too short to evaluate the impact of rifaximin therapy on the development of OHE, it was noted that 1 patient receiving rifaximin and 2 patients receiving placebo developed OHE.⁹

The risk of developing OHE is 3.7-fold greater for cirrhotic patients who have been diagnosed with CHE than in those without this diagnosis. Over a period of 3 years, 56% of patients with CHE developed OHE compared with 8% of those without CHE.¹⁰ It may therefore be judicious to limit primary therapy to those most at risk (ie, those with CHE). One factor that has impeded this approach, however, is that no consensus on diagnostic criteria or diagnostic tests for CHE has been established.¹¹

Table 1 lists tests that have been utilized in the diagnosis of CHE along with their advantages and limitations.² While testing may be performed at medical centers with transplant units and for research purposes, most cirrhotic patients in community practice are not routinely tested because of time constraints, lack of psychological expertise, cost, and copyright issues.^{1,12} This may change with the introduction of 2 computerized tests that appear practical for use in office-based medical practices. Both tests have been adapted for assessing neurocognitive function in cirrhotic patients from tests used in the diagnosis of other medical and psychiatric conditions. Use of the Inhibitory Control Test (ICT) for the diagnosis of CHE was first described by Bajaj et al.¹³ Results of the ICT test were compared with

a battery of standard psychometric tests (ie, Number Connection Test-A, Digit Symbol Test, Block Design Test). The ICT was reported to have a sensitivity of 87% and a specificity of 77% for the diagnosis of CHE; the receiver operating characteristic curve had an area under the curve of 0.902. The authors concluded that ICT is a sensitive, reliable, and valid test for CHE diagnosis that can be administered by medical assistants.¹³ The ICT test is available free of charge online at <http://www.hecme.tv>. Registration with the HEcmeTV Website is required in order to use the ICT.

Methods	Advantages	Limitations
Formal neuropsychological assessment	Established and well-recognized clinical significance	- Expensive - Time consuming
Short neuropsychological batteries	- Easy to administer in office setting - Inexpensive - Rapid results - High sensitivity for discerning CHE from other encephalopathies	- Test often copyrighted - Limited access
Computerized tests (CFF, ICT, reaction times, etc)	Easy to apply	- Limited data on diagnostic significance - Require standardization
Neurophysiologic tests (EEG, spectral EEG, P300)	Allows for objective repeat testing	- Equipment - Limited data on diagnostic significance

Table 1. Neuropsychological and neurophysiologic tests that have been used in the diagnosis of CHE. CFF, critical flicker frequency; ICT, inhibitory control test; EEG, electroencephalography; P300, auditory event-related evoked potential.²

A second computerized test appropriate for use in diagnosing CHE in the office-based setting was described in a presentation at DDW 2012. This test utilized the CNS Vital Signs (CNSVS) psychometric test battery. Cirrhosis patients were first screened with the mini-mental status examination and a thorough neurological examination to exclude those with OHE; 100 patients met enrollment criteria. This was followed by administration of the Psychometric Hepatic Encephalopathy Score (PHES) test battery (ie, Digit Symbol Test, Number Connection Tests A and B, Serial Dotting Test) and the CNSVS battery. Matched healthy controls (n=110) were used for obtaining PHES normative data. A high correlation of 0.60 ($P<.001$, 95% CI 0.45–0.74) was observed between the PHES and CNSVS test results. The CNSVS battery was able to diagnose CHE with 85% sensitivity and 64% specificity; the receiver operating characteristic curve had an area under the curve of 0.74. The authors concluded that the CNSVS battery is a sensitive and reliable psychometric testing system for the diagnosis of CHE.¹⁴ The test is available online at <http://www.cnsvs.com>, and test results are available immediately after the test. A free trial test is available for those who register with the CNSVS Website.

Secondary prophylactic therapy for prevention of recurrence of OHE in cirrhotic patients who have experienced an OHE episode

In-hospital management of OHE involves identification and correction and/or removal of underlying precipitating factors and treatment aimed at reducing the production and absorption of ammonia in the

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gut. After an episode of OHE has resolved, patients with cirrhosis should receive secondary prophylactic therapy for an indefinite period of time or until they undergo liver transplantation.¹⁵ Both lactulose and rifaximin are effective when used to prevent recurrence of OHE in cirrhotic patients who have experienced an OHE episode.¹⁶

Sharma et al published the results of a recent open-label study of lactulose versus placebo for preventing recurrence of OHE in cirrhotic patients that reaffirmed the utility of lactulose as a secondary prophylactic therapy. The study was open-label because treatment with lactulose causes diarrhea, thus making it impossible to remain blind to who is receiving the active study drug. Cirrhotic patients who recovered from OHE were randomized within 1 week following recovery to receive either lactulose (n=70) or placebo (n=70). The lactulose patients received 30 to 60 mL of lactulose in 2 or 3 divided doses per day so that they passed 2 to 3 semisoft stools per day. The primary endpoint was development of OHE. Treatment was continued until the primary endpoint was achieved or for a minimum of 6 months; 61 patients in the lactulose group and 64 patients in the placebo group were followed up for a median of 14 months. Twelve of 61 patients (19.6%) in the lactulose group and 30 of 64 patients (46.8%) in the placebo group developed OHE ($P=.001$). Figure 1 illustrates graphically the probability of developing recurrent OHE in patients receiving lactulose compared with those receiving placebo.

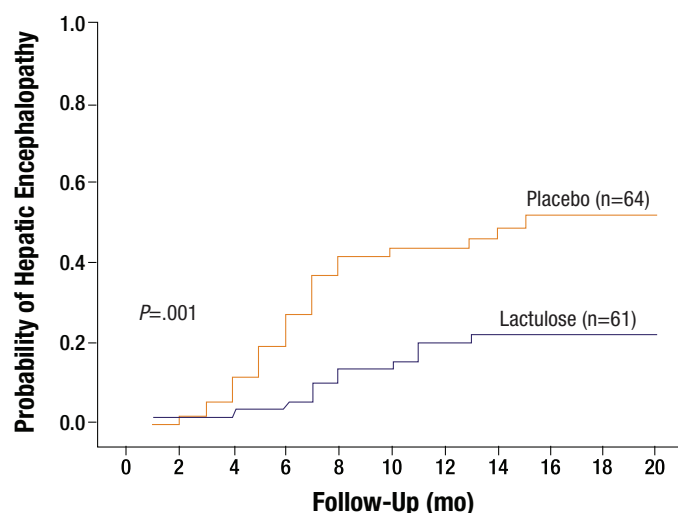


Figure 1: Probability of developing recurrent OHE in patients receiving prophylactic therapy with lactulose following an episode of OHE compared with patients receiving placebo.⁷

All patients receiving lactulose remained adherent to therapy. Of 61 patients, 14 (23%) had diarrhea, 6 (10%) had abdominal bloating, and 8 (13%) had a distaste for lactulose; the dose of lactulose was reduced but not stopped in these patients. The authors concluded that lactulose is effective for the prevention of recurrence of OHE in cirrhotic patients.⁷

While Sharma et al found patients adherent to lactulose therapy in their clinical trial, others have reported that the excessively sweet taste and gastrointestinal side effects such as bloating, flatulence and severe and unpredictable diarrhea result in frequent nonadherence in clinical practice.¹⁷ The results of a retrospective study of 109 cirrhotic patients with a total of 200 hospital admissions with a primary

diagnosis of OHE were reported at DDW 2012. The study focused on precipitants of OHE. One precipitant was found in 86 (43%) admissions, 2 precipitants were found in 84 (42%), 3 precipitants in 26 (13%), and 4 (2%) precipitants in 4 admissions. Lactulose nonadherence, reported as a factor in 39% of hospital admissions, was the single most frequent precipitant (Table 2). The authors concluded that patient and family education regarding lactulose dosing and avoidance of precipitating drugs and dehydration will potentially reduce a number of hospital admissions due to recurrence of OHE.¹⁸

Precipitating Factor	Frequency per 200 Admissions	Percentage
Lactulose nonadherence	78	39
Constipation	44	22
Opioids and benzodiazepines	34	17
Dehydration	32	16
Infections	30	15
Acute renal failure	17	8.5
Hypokalemia (potassium <3.5)	14	7
Gastrointestinal bleeding	12	6
Large volume paracentesis	4	2
TIPS	4	2
Hyponatremia (sodium <130)	4	2
High protein diet	2	1
Unknown precipitants	18	9

Table 2: Factors identified as precipitants of OHE in 109 cirrhotic patients who had 200 hospital admissions with a primary diagnosis of OHE. TIPS, transjugular intrahepatic portosystemic shunt.¹⁸

Rifaximin can also be used for secondary prophylaxis against recurrence of OHE in patients who have recovered from an episode of OHE. Rifaximin is a minimally absorbed oral antibiotic with broad-spectrum activity against gram-positive and gram negative aerobic and anaerobic enteric bacteria. Rifaximin has a low risk of inducing bacterial resistance. Bass et al published the results of a randomized, double-blind, placebo-controlled study comparing rifaximin (140 patients) with placebo (159 patients) when used for secondary prophylaxis in cirrhotic patients who were in remission from recurrent OHE. Patients received either rifaximin at a dose of 550 mg twice daily or placebo for 6 months; 90% of patients in both the rifaximin arm and the placebo arm also received concomitant lactulose therapy. The primary efficacy endpoint was the time to the first breakthrough episode of OHE. A breakthrough episode of OHE occurred in 31 of 140 patients (22.1%) in the rifaximin group and in 73 of 159 patients (45.9%) in the placebo group, reflecting a relative reduction in the risk of breakthrough by 58% with rifaximin as compared with placebo during the 6-month study period. A Kaplan-Meier analysis of time to the first breakthrough OHE episode is depicted in Figure 2. The incidence of adverse events and the more common serious adverse events reported during the study was similar for the rifaximin group and the placebo group.¹⁷

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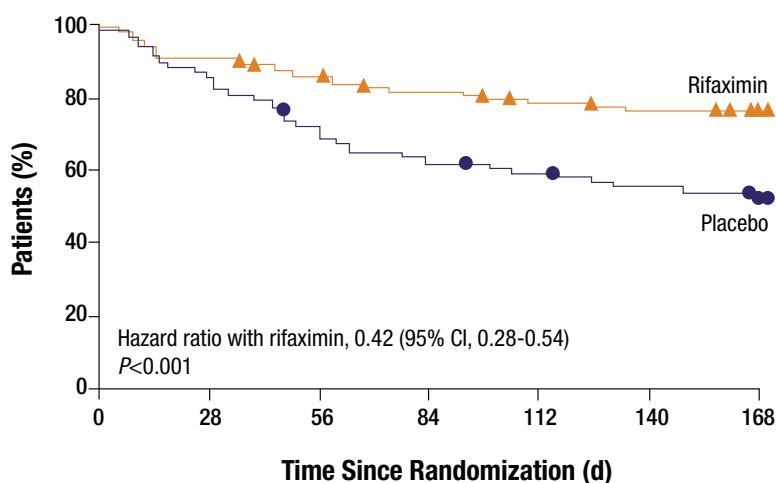


Figure 2. Time to first breakthrough OHE episode in patients receiving prophylactic therapy with rifaximin following an episode of OHE compared to patients receiving placebo.¹⁷

Upon completion of the trial described above, 75 patients from the rifaximin arm, 82 patients from the placebo arm, and 170 new patients with recurrent OHE were enrolled in a 24-month open-label maintenance trial of rifaximin to assess long-term efficacy and safety. Results from the open-label maintenance trial were presented at DDW 2012. Long-term event rates for breakthrough OHE episodes (events/person exposure years) remained low and were 0.3 for the 82 placebo patients crossed over to rifaximin, 0.4 for the 252 patients new to rifaximin, and 0.24 for the 70 continuing rifaximin patients. All OHE breakthrough rates were similar to the randomized controlled trial rifaximin arm rate of 0.6 and significantly lower than the randomized controlled trial placebo group rate of 1.59 ($P < .0001$). Safety was not adversely affected with long-term rifaximin exposure, and adverse event rates remained stable in the long-term. The authors concluded that long term treatment with rifaximin 550 mg twice daily afforded continued protection from recurrent OHE without adversely affecting safety.¹⁹

Currently, lactulose and rifaximin are the preferred choices for secondary prophylactic therapy in patients for the prevention of recurrent OHE. Both compounds have proven efficacy and act by reducing the production and/or absorption of ammonia in the gut. The search continues, however, to find prophylactic therapies with even greater efficacy. Preliminary results of a study utilizing glyceryl tri-(4phenylbutyrate) (GPB) in cirrhotic patients with episodic OHE and >2 recent OHE events were reported at DDW 2012. GPB lowers blood ammonia levels by increasing urinary excretion of nitrogen. GPB was dosed at 6 mL twice daily for 1 week followed by 9 mL twice daily for 3 weeks. Fifteen subjects were enrolled in the study and 8 completed the study. On day 1, mean ammonia decreased from 74.4 mcg/dL predose to 65.1 mcg/dL at 4 hours post-first-dose. Fasting ammonia was lower on GPB on all assessment days compared with baseline with the greatest decrease (to 45.4 mcg/dL) on day 7 of the 6 mL twice daily dosing. The 9 mL twice daily dosing resulted in similar ammonia lowering but was associated with more adverse events. The authors concluded that the 6 mL twice daily GPB dose was appropriate for further evaluation in patients with cirrhosis and episodic OHE.²⁰

Summary

It is now recognized that neurocognitive impairment associated with an episode of OHE in cirrhotic patients may not be completely reversible following apparent recovery. Recent studies have documented persistent and cumulative deficits in working memory and learning following OHE. Prevention of OHE is therefore warranted. Therapy administered before an episode of OHE is referred to as primary prophylaxis, and this therapy might best be reserved for patients diagnosed with CHE. Cirrhotic patients with CHE have a 3.7 fold greater risk for developing OHE than non-CHE patients with cirrhosis. Both lactulose and rifaximin are effective for primary prophylaxis. One factor that has limited the use of primary prophylaxis against OHE has been the difficulty in diagnosing CHE in office-based practice settings. The ICT and the CNSVS computerized tests for assessing neurocognitive function in cirrhotic patients have recently become available online; both tests are suitable for use in the community setting.

Since neurocognitive deficits following OHE may be cumulative, prophylactic therapy following recovery from an episode of OHE is essential. Drug therapy administered long-term following recovery from OHE to prevent recurrence is referred to as secondary prophylactic therapy. Clinical studies have demonstrated the effectiveness of both lactulose and rifaximin when used for the prevention of recurrence. Diarrhea is a common side effect of lactulose therapy and may decrease patient adherence. The side effect profile of rifaximin is similar to placebo.

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Required with 70% passing.

1. **The annual risk of developing overt hepatic encephalopathy (OHE) in cirrhotic patients is:**
 - a. Less than 10%
 - b. Approximately 20%
 - c. Approximately 60%
 - d. Greater than 80%
2. **Which term best describes recovery of neurocognitive impairment following an episode of overt hepatic encephalopathy (OHE):**
 - a. It is completely irreversible
 - b. It is completely reversible within days
 - c. It is completely reversible, but may take months
 - d. It may be associated with persistent and cumulative deficits
3. **Which of the following is a computerized test, available online, that can be used in an office-based practice for diagnosing covert hepatic encephalopathy (CHE) in cirrhotic patients?**
 - a. Number Connection Tests A and B
 - b. Digit Symbol Test
 - c. Psychometric Hepatic Encephalopathy Score (PHES) test battery
 - d. CNS Vital Signs (CNSVS) psychometric test battery
4. **A retrospective study of 109 cirrhotic patients with a total of 200 hospital admissions for overt hepatic encephalopathy (OHE) found that the most frequent precipitant for OHE was:**
 - a. Use of opioids and benzodiazepines
 - b. Infections
 - c. Lactulose noncompliance
 - d. High protein diet
5. **The Sharma study comparing lactulose vs. placebo for preventing recurrence of overt hepatic encephalopathy (OHE) was an open-label as opposed to a blinded trial because patients could identify the active drug due to:**
 - a. Diarrhea
 - b. Constipation
 - c. Nausea and vomiting
 - d. Bitter taste
6. **The 24-month open-label maintenance trial of rifaximin in cirrhotic patients for the prevention of recurrent overt hepatic encephalopathy (OHE) found that the long-term event rate for breakthrough overt hepatic encephalopathy (OHE) episodes (events/person exposure years):**
 - a. Gradually increased over time
 - b. Gradually decreased over time
 - c. Were similar to the randomized controlled trial rifaximin arm
 - d. Could not be determined because of the development of bacterial resistance

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Purdue University College of Pharmacy respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form.

	<i>This learning objective did (or will) increase/improve my:</i>	<i>High Impact</i>	<i>Moderate Impact</i>	<i>No Impact</i>	<i>Not Applicable</i>
Recognize that elements of neurocognitive impairment associated with overt hepatic encephalopathy may be irreversible and cumulative, thus warranting prophylactic therapy in cirrhotic patients at risk for developing this complication of advanced liver disease	Knowledge	☐	☐	☐	☐
	Competence	☐	☐	☐	☐
	Performance	☐	☐	☐	☐
	Patient Outcomes	☐	☐	☐	☐
Identify computerized tests for neurocognitive function that are appropriate for use in community-based clinical practice for diagnosing covert hepatic encephalopathy	Knowledge	☐	☐	☐	☐
	Competence	☐	☐	☐	☐
	Performance	☐	☐	☐	☐
	Patient Outcomes	☐	☐	☐	☐
Assess the efficacy and tolerability of lactulose and rifaximin as primary and secondary prophylactic agents for preventing overt hepatic encephalopathy	Knowledge	☐	☐	☐	☐
	Competence	☐	☐	☐	☐
	Performance	☐	☐	☐	☐
	Patient Outcomes	☐	☐	☐	☐

Impact of the Activity

- Please indicate which of the following American Board of Medical Specialties/Institute of Medicine core competencies were addressed by this educational activity (*select all that apply*):

- | | | |
|--|--|--|
| ☐ Patient care or patient-centered care | ☐ Interdisciplinary teams | ☐ System-based practice |
| ☐ Practice-based learning and improvement | ☐ Professionalism | ☐ Utilize informatics |
| ☐ Interpersonal and communication skills | ☐ Quality improvement | ☐ None of the above |
| ☐ Employ evidence-based practice | ☐ Medical knowledge | |

- The content of this activity matched my current (or potential) scope of practice.

- ☐ No _____
- ☐ Yes, please explain _____

- Was this activity scientifically sound and free of commercial bias* or influence?

- ☐ Yes _____
- ☐ No, please explain _____

* Commercial bias is defined as a personal judgment in favor of a specific product or service of a commercial interest.

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	Strongly Agree	Agree	Disagree	Strongly Disagree	Not Applicable
• The educational activity has enhanced my professional effectiveness in treating patients	☐	☐	☐	☐	☐
• The educational activity will result in a change in my practice behavior	☐	☐	☐	☐	☐
• How will you change your practice as a result of participating in this activity (<i>select all that apply</i>)?					
☐ Create/revise protocols, policies, and/or procedures ☐ Change the management and/or treatment of my patients ☐ This activity validated my current practice	☐ I will not make any changes to my practice ☐ Other, please specify: _____ _____				
• What new information did you learn during this activity?					

• Please indicate any barriers you perceive in implementing these changes.					
☐ Lack of experience ☐ Lack of resources (equipment) ☐ Lack of time to assess/counsel patients ☐ Lack of consensus of professional guidelines ☐ Lack of opportunity (patients) ☐ Lack of administrative support	☐ Reimbursement/insurance issues ☐ Patient compliance issues ☐ No barriers ☐ Cost ☐ Other _____ _____				
• If you indicated any barriers, how will you address these barriers in order to implement changes in your knowledge, competency, performance, and/or patients' outcomes?					

• Comments to help improve this activity?					

• Recommendations for future CME/CPE topics.					

To assist with future planning, please attest to time spent on activity:					
I spent _____ hours on this program					

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