Hepatic Encephalopathy Update: Reports From ACG 2012 and The Liver Meeting 2012

HEPATOLOGY Centers of Educational Expertise

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Objectives:

After reading and studying this newsletter, the participant should be able to:

- Assess emerging new therapies for the treatment of acute overt hepatic encephalopathy and as secondary prophylactic agents for the prevention of recurrence of overt hepatic encephalopathy
- Evaluate long-term rifaximin efficacy and safety data as secondary prophylactic therapy for overt hepatic encephalopathy
- Describe survival probability of patients who have experienced overt hepatic encephalopathy and how choice of secondary prophylactic treatment may affect survival probability

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Overt hepatic encephalopathy (OHE), along with ascites and esophageal and gastric varices, is a primary complication of cirrhosis of the liver. An estimated 5.5 million people in the United States have hepatic cirrhosis and, of these, 30% to 45% will develop OHE.[1] The burden of cirrhosis is increasing in the United States. Hospital discharges due to cirrhosis (all listed diagnoses) increased by 6% from 2009 (498,181 patients) to 2010 (526,096 patients). While it is difficult to estimate the true incidence of OHE, it appears to be increasing at an even higher rate than cirrhosis. During the same time period, hospital discharges for hepatic encephalopathy (all listed diagnoses) increased by 21% from 2009 (345,887 patients) to 2010 (419,389 patients).[2]

The development of OHE in those with cirrhosis is an unfavorable sign. Without appropriate prophylactic therapy to prevent recurrence and/or the patient having had a liver transplant, the survival probability is 42% at 1 year and 23% at 3 years.[3] The first step in managing the acute stage of OHE involves identifying and treating the precipitating cause. Precipitating causes include hypovolemia, gastrointestinal bleeding, infection, dehydration secondary to diuretic use, diarrhea, vomiting, hyponatremia, hypokalemia or hyperkalemia, alkalosis, surgery, renal failure, transjugular intrahepatic portosystemic shunt, constipation, benzodiazepine use, narcotic use, hypoxemia, hepatoma, and noncompliance with lactulose therapy.[4]

Simultaneously with identification and correction of the precipitating cause, therapy aimed at reducing the nitrogenous load in the intestine to reduce the accumulation of ammonia is instituted. Ammonia is thought to play a major role in the pathogenesis of hepatic encephalopathy. The cirrhotic liver is unable to metabolize ammonia formed when protein is broken down by bacteria in the intestines, resulting in an increase in serum ammonia. Uptake of ammonia by astrocytes causes cerebral edema and resultant neurologic dysfunction.[1, 4, 5] The two primary therapies currently used to reduce circulating ammonia are the nonabsorbable disaccharide, lactulose, and the nonabsorbable antibiotic, rifaximin. Either agent can be used during the acute stages of OHE and lactulose, rifaximin, or combination lactulose/rifaximin should be used prophylactically following recovery from OHE to prevent recurrence. Prophylactic therapy, referred to as secondary prophylaxis when instituted to prevent recurrence of OHE following an OHE episode, should continue for an indefinite period or until liver transplantation.[1, 4, 6]

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This newsletter will review several selected presentations from ACG 2012* and The Liver Meeting 2012† to heighten awareness of advances in the treatment of OHE.

Polyethylene glycol 3350-electrolyte solution (PEG) vs. lactulose for patients hospitalized with acute OHE

Lactulose has been used to reduce serum ammonia concentrations in patients with OHE. Lactulose acidifies the fecal stream, causing protonation of ammonia (NH_3) into ammonium ions (NH_4^+). Absorption of the charged NH_4^+ ions is limited, causing NH_4^+ to remain trapped in the colonic lumen. The cathartic action of lactulose can also enhance elimination of ammonia.[4] Animal studies suggested that polyelthylene glycol 3350-electrolyte solution (PEG; Golytely®) may be effective at clearing intestinal bacteria and reducing bacterial ammoniagenesis. Rahimi et al compared the effects of lactulose (n=25) and PEG (n=25) in hospitalized patients with acute OHE.[8] Patient demographics, clinical characteristics, and laboratory values were similar in both arms of the study. Severity of OHE was assessed using the hepatic encephalopathy scoring algorithm (HESA), which combines clinical impressions with neuropsychological performances to characterize OHE. Study results are summarized in Table 1.

	Lactulose (mean ± SD) n=25	*PEG (mean ± SD) n=23*	*P* value
Baseline HESA	2.3 ± 0.8	2.3 ± 0.9	0.787
24 hour HESA	1.6 ± 0.9	0.9 ± 1	0.015
Overall response within 24 hours (%)	52	91	0.002
Length of stay	7.8 ± 12	3.7 ± 3.5	0.110

Table 1. Effect of lactulose vs. PEG treatment on 24-hour hepatic encephalopathy scoring algorithm (HESA), overall response, and length of hospitalization in patients with acute OHE.[8]

Both the 24- hour HESA score and the percent of patients with an overall response (absolute difference in HESA score at 24 hours; improvement in one HESA grade accounts for an overall response) were significantly better in the PEG group than in the lactulose group. The mean hospital length of stay, while it did not reach a statistically significant difference, was more than twice as long with lactulose (7.8 days) when compared to PEG (3.7 days). The authors concluded that PEG may be superior to lactulose for treatment of patients hospitalized for acute OHE.

*ACG 2012: American College of Gastroenterology 2012 Annual Scientific Meeting and Postgraduate Course. Las Vegas, NV. October 19-24, 2012.
†The Liver Meeting 2012: The 63rd Annual Meeting of the American Association for the Study of Liver Diseases. Boston, MA. November 9-13, 2012.

Glycerol phenylbutyrate (GPB) as secondary prophylactic therapy in patients with episodic OHE

GPB is an investigational drug which lowers serum ammonia (NH_3) through metabolism to phenylacetylglutamine, a urea surrogate that is excreted in urine. Rockey et al investigated the effect of GPB in a randomized, placebo-controlled, double-blind study of patients with ≥2 OHE episodes in the prior 6 months while on standard of care (SOC) including lactulose and/or rifaximin.[9] Patients received GPB (6 mL BID; n=90)) or placebo (n=88) for 16 weeks, while continuing to receive SOC background treatment. The primary endpoint was the proportion of patients with ≥1 OHE event; secondary endpoints included total OHE events, hospitalizations, symptomatic days assessed using Clinical Hepatic Encephalopathy Staging Scale (CHESS) and venous NH_3. Study results are summarized in Table 2.

	All Patients			*Rifaximin naïve (n=119)*			*Rifaximin at Baseline (n=59)*		
	GPB (N=90)	Placebo (N=88)	*P* value	GPB (n=60)	Placebo (N=59)	*P* value	GPB (n=30)	Placebo (n=29)	*P* value
At least one OHE event (ITT)	21% (19/90)	36% (32/88)	0.021	10% (6/60)	32% (19/59)	0.003	43% (13/30)	45% (13/29)	NS
Total OHE events	35	57	0.035	7	31	<0.001	28	26	NS
Days with CHESS* score ≥3	13	27	0.015	---	---	---	---	---	---
OHE hospitalizations	13	25	0.064	---	---	---	---	---	---
OHE hospital days	66	134	NS	---	---	---	---	---	---
NH_3 time-normalized AUC (µmol)	46	58	0.036	36	43	0.08	67	91	0.13
Subjects reporting AEs	79%	76%	NS	---	---	---	---	---	---

*CHESS, Clinical Hepatic Encephalapothy Staging Scale.

Table 2. Effects through week 16 of glyceryl phenylbutyrate (GPB) vs. placebo in all patients with advanced liver disease and in the rifaximin-naïve and rifaximin-experienced subsets. All patients had recovered from ≥2 OHE episodes while on standard of care (lactulose and/or rifaximin); standard of care was continued as background treatment during study.[9]

The percentage of patients receiving GPB with at least one OHE episode was significantly reduced compared to placebo (21% GPB vs. 36% placebo). Patients receiving GPB, compared to placebo, also had significant reductions in total OHE events (35 GPB vs. 57 placebo), days with CHESS score ≥3 (13 GPB vs. 27 placebo), and time normalized NH_3 AUC (46 GPB vs. 58 placebo). Changes in total OHE hospitalizations and total OHE hospitalization days, although reduced in the GPB group compared to the placebo group, were not statistically significant. The percentages of patients reporting adverse advents were similar in the GPB (79%) and placebo (76%) study arms. Interestingly, GPB had a strong treatment effect in patients who were not on rifaximin at baseline, but had little effect in those who were receiving rifaximin at baseline. The authors concluded that GPB shows promise as a secondary prophylactic agent for the prevention of recurrent OHE with a strong treatment effect in non-rifaximin patients and the potential for incremental benefit in rifaximin patients.

A probiotic preparation for secondary prophylaxis of OHE in cirrhotic patients

A recent Cochran Database System review of clinical studies that used probiotics for the treatment of OHE questioned their efficacy in altering clinically relevant outcomes.[10] Dhiman et al conducted a study to 'demonstrate the unequivocal efficacy of a probiotic preparation for the prevention of OHE recurrence, the reduction in hospitalizations, and for improving the severity of liver disease in cirrhotic patients.[11] The randomized, double-blind, placebo-controlled trial involved patients with liver cirrhosis who recovered from an OHE episode during the previous 1 month. Patients received either a probiotic preparation (VSL#3, which contained *Streptococcus thermophilus, Bifidobacterium breve, Bifidobacterium longum,*

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Bifidobacterium infantis, Lactobacillus plantarum, Lactobacillus paracasei, and Lactobacillu bulgaricus) or placebo for 6 months. VSL#3 was administered at a dose of 900 billion bacteria daily to 51 patients; 52 patients received placebo. The study results are presented in Table 3.

	VSL#3 Probiotic (n=51)	*Placebo (n=52)*	*P* value
Breakthrough OHE	25.5%	36.5%	0.258
Overall hospitalizations	19.6%	42.3%	0.036
OHE-related hospitalizations	15.7%	34.6%	0.037
Child-Turcotte-Pugh score (baseline → 6 months)	8.7 → 7.2 (P=0.009)	8.6 → 7.6 (NS)	---
Serum interleukin-6 (pg/mL)	60.3 → 33.4 (P=0.007)	82.5 → 38 (P=0.09)	---
Death	21.6%	17.3%	---

Table 3. Effects of administration of VSL#3 probiotic for 6 months vs. placebo in patients who have recovered from an episode of OHE during previous 1 month.[11]

While fewer patients treated with probiotic (25.5%) had breakthrough OHE compared to placebo (36.5%), the difference was not statistically significant. Overall hospitalizations for probiotic vs. placebo (19.6% vs. 42.3%) and OHE-related hospitalizations for probiotic vs. placebo (15.7% vs. 34.6%) were significantly different. When comparing 6-month values with baseline values, significant improvements were seen in the Child-Turcotte-Pugh score (8.7 → 7.2) and in serum interleukin-6 levels (60.3 pg/mL → 33.4 pg/mL) in patients receiving probiotic; changes in the Child-Turcotte-Pugh score and in serum interleukin-6 concentrations were not statistically significant in patients receiving placebo. The authors concluded that secondary prophylactic treatment with the probiotic VSL#3 of patients who had recovered from an OHE episode significantly reduced the risk of overall hospitalizations including those involving OHE and also significantly reduced Child-Turcotte-Pugh scores and serum interleukin-6 concentrations. While breakthrough OHE was reduced, the change was not statistically significant.

Long-term use of rifaximin as secondary prophylaxis for the prevention of recurrence of OHE

In a 6-month study, rifaximin prophylactic therapy reduced the risk of OHE recurrence in cirrhotic patients with a history of OHE by 58% compared to placebo. OHE-related hospitalizations were also reduced.[12] Since secondary prophylactic therapy should be continued indefinitely or until liver transplant, a long-term, open-label extension study was conducted to examine the long-term efficacy and safety of rifaximin. Bajaj et al reported on the long-term outcomes of a subset of patients (n=82) who were in the placebo arm of the 6-month study and who crossed over to rifaximin (550 mg twice daily) in the open-label extension study.[13] The total person-years of exposure was 134.2. Maintenance of remission was maintained for up to 840 days in some patients. The OHE breakthrough event rate and OHE-related hospitalization event rate were significantly lower after crossover than the corresponding event rates during prior placebo treatment ($P<0.0001$ and $P<0.01$, respectively; Figure 1). The rates of the most common treatment-emergent adverse events in placebo crossover patients were similar to those observed in the placebo arm of the 6-month study (Table 4). Similarly, rates of infection in the placebo crossover patients were comparable to rates observed in the 6-month study with the exception of pneumonia, which was not seen in placebo patients during the 6-month trial (Table 4). The authors concluded that rifaximin therapy for up to 840 days in cirrhotic patients who had received placebo in the 6-month study reduced the risk of OHE recurrence and OHE-related hospitalizations without increasing the rates of adverse events or infections.

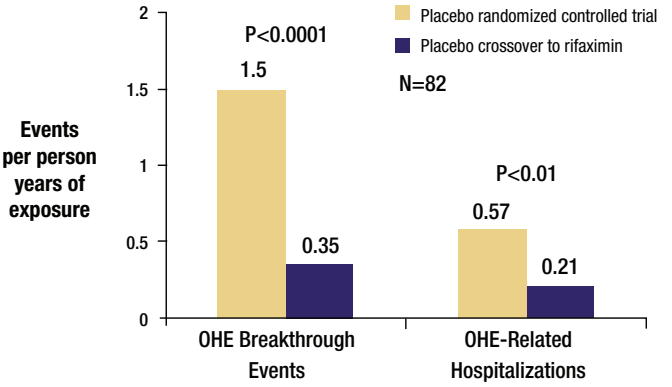

Figure 1. OHE breakthrough events and OHE-related hospitalizations in patients receiving placebo for 6 months and then crossed over to receive rifaximin long-term (up to 840 days).[13]

Adverse events, n (rate)*	*Six Month trial*	*Long-term*
	Placebo (n=82) PYE†=26.2	*Crossover to Rifaximin (n=82) PYE† = 134.2*
Incidence and rate of treatment-emergent adverse events		
Peripheral edema	9 (0.36)	18 (0.16)
Nausea	11 (0.47)	17 (0.14)
Dizziness	8 (0.33)	7 (0.06)
Fatigue	8 (0.32)	8 (0.06)
Incidence and rate of infections		
Cellulitis	2 (0.08)	11 (0.09)
Intestinal infections	0 (0)	1 (0.007)
Peritonitis	3 (0.11)	5 (0.04)
Pneumonia	0 (0)	10 (0.08)
Sepsis/septic shock	2 (0.08)	10 (0.08)
Urinary tract/ kidney infection	7 (0.29)	14 (0.12)

*Rate is calculated as number of patients with particular adverse event ÷ total person-years of Exposure.
†PYE = total person-years of exposure.
TEAEs = treatment-emergent adverse events occurring in ≥10% of patients in placebo arm of 6-month trial.

Table 4. Incidence and rate of most common treatment-emergent adverse events and incidence and rate of infections in patients treated with placebo for 6 months compared to the incidences and rates in the same patients following crossover to rifaximin for up to 840 days.[13]

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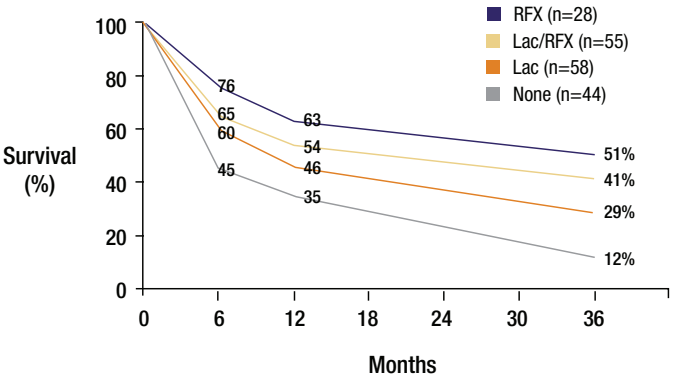
Long-term survival following overt hepatic encephalopathy

Long-term survival data for patients with OHE is rather limited.[3] A retrospective study by Neff et al provides updated survival data not only for those who received no secondary prophylactic therapy, but also differentiates post-OHE survival in those who received secondary prophylactic therapy according to the agent(s) utilized.[14] Medical charts of patients admitted to a large transplant program between December 2000 and May 2012 were examined. Four groups were identified including patients receiving lactulose monotherapy (n=58), patients receiving lactulose combined with rifaximin (n=55), patients receiving rifaximin monotherapy (n=28), and patients receiving no secondary prophylactic therapy (n=44). Data collected included post-discharge HE management protocol and time to transplant or death.



Lac vs. Lac/RFX, *P*=0.057; Lac vs. RFX, *P*=0.049

Figure 2. Long-term survival following OHE according to secondary prophylactic therapy received post-discharge from the hospital.[14]

The results are illustrated graphically in Figure 2. At each time point, survival with rifaximin monotherapy > survival with lactulose/rifaximin combination therapy > survival with lactulose monotherapy > survival with no secondary prophylactic therapy for recurrent OHE. Survival differences between the lactulose group and the rifaximin group were significant (*P*=0.049). The authors concluded that rifaximin, either as monotherapy or in combination with lactulose, improves both short- and long-term survival compared to lactulose monotherapy or to no therapy when used as secondary prophylaxis for recurrent OHE.

Secondary prophylactic treatment patterns in patients following an episode of OHE

Practice guidelines for the treatment of OHE have never been issued by the American Association for the Study of Liver Diseases or the American Gastroenterological Association, and the guidelines issued by the American College of Gastroenterology (ACG) published in 2001 are outdated.[15] While the ACG guidelines list 'Assessment of the Need for Long Term Therapy' as a treatment goal, no specific recommendations are provided. Experts in the field, however, recommend treatment with lactulose monotherapy, rifaximin monotherapy, or lactulose/rifaximin combination therapy as secondary prophylactic therapy following recovery from the acute stages of OHE.[1, 4, 6] Secondary prophylactic therapy should be continued for an indefinite period of time or until liver transplantation.[1, 4, 6] A retrospective review of a subset of national claims for medical and hospital activity from January 2009 to December 2011 suggests, however, that most OHE patients are not currently receiving secondary prophylactic therapy.[16] In the review, patient selection was based on claims with an ICD-9 code 572.2 (HE). Claims from eligible patients were reviewed for any filled prescriptions for rifaximin, lactulose, or rifaximin/lactulose combination therapy. A total of 13,623; 15,529; and 16,328 patients were identified for 2009, 2010, and 2011, respectively. Treatment patterns observed are summarized in Table 5. Surprisingly, the percentage of OHE patients receiving either inpatient therapy with lactulose, rifaximin, or rifaximin/lactulose actually decreased over the 2009 to 2011 sample interval from 89.2% to 86.4%. The percentage of patients receiving secondary prophylactic therapy after hospital discharge following an OHE episode also decreased over the sample interval from 39.7% to 36.1%. Another finding in the OHE treatment study was that the approval of rifaximin for the treatment of recurrence of OHE in 2010 changed the choice of therapy for OHE from 2009 to 2011, with a reduction in the percentage of patients receiving lactulose monotherapy (27.9% → 14.1%) and an increase in the percentages receiving either rifaximin monotherapy (3.9% → 13.2%) or rifaximin/lactulose combination therapy (8.1% → 8.8%). The authors were unable to identify the cause of the low treatment rates, but suggested the reason may be a failure of patients to fill prescriptions (lack of insurance, other financial concerns, and/or noncompliance) and/or healthcare providers not being adequately educated about the benefits of treatment.

	2009	2010	2011
Eligible patients identified (n)	13,623	15,529	16,328
Patients with inpatient claims (%)	89.2%	87.8%	86.4%
Patients receiving ongoing treatment (%)	39.7%	37.7%	36.1%

Table 5. Review of a subset of filled prescription claims (rifaximin, lactulose, and rifaximin/lactulose combination therapy) for patients with an ICD-9 code 572.2 (HE) while they were hospitalized and following recovery.[16]

Summary

The burden of hepatic cirrhosis and OHE in the United States is increasing. Promising advances in the treatment of OHE are taking place as indicated in this review of selected presentations from ACG 2012 and The Liver Meeting 2012. Polyethylene glycol 3350-electrolyte solution (Golytely®) may emerge as an alternative to lactulose in the treatment of acute episodes of OHE. Glycerol phenylbutyrate, which enhances urinary excretion of a metabolite of urea, thus lowering serum concentrations of urea, significantly decreased OHE episodes when compared to placebo; changes in OHE hospitalizations and total hospitalization days, although fewer in number compared to placebo, were not statistically significant. In contrast, treatment with the probiotic VSL#3 produced significant reductions in OHE hospitalizations and total hospitalization days when compared to placebo, but the effect of VSL#3 on breakthrough OHE compared to placebo was not significant. Long-term administration of rifaximin (up to 840 days) in patients who had received placebo in a 6-month study prior to crossover significantly reduced the risk of OHE recurrence and OHE-related hospitalization without increasing the

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rates of adverse events or infections. Although experts recommend continuation of secondary prophylactic therapy with lactulose, rifaximin, or lactulose/rifaximin therapy for an indefinite period of time or until liver transplantation, a retrospective review of patient records suggests that only one-third of patients actually receive long-term prophylaxis following recovery from an OHE episode.

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Required with 70% passing.

1. Which of the following agents lowers serum ammonia through metabolism to a urea surrogate that is excreted in the urine?

a. Rifaximin

b. Lactulose

c. Polyethylene glycol 3350-electrolyte solution

d. Glycerol phenylbutyrate

2. In the study by Dhiman et al, the probiotic VSL#3 was statistically significantly better in all of the following except:

a. Breakthrough overt hepatic encephalopathy compared to placebo

b. Overall hospitalizations compared to placebo

c. Overt hepatic encephalopathy-related hospitalizations compared to placebo

d. Improvement in Child-Turcotte-Pugh score at 6 months compared to baseline

3. When compared to rates observed during a 6- month study in which they received placebo, patients who were crossed over to rifaximin in a long-term extension study:

a. Had an increase in the rates for the most common treatment-emergent adverse events

b. Had a decrease in the rates for cellulitis, intestinal infections, pneumonia, and sepsis/septic shock

c. Had a decrease in the rate of overt hepatic encephalopathy breakthrough events

d. Had an increase in the rate of overt hepatic encephalopathy-related hospitalizations

4. A retrospective study of long-term survival for patients following recovery from overt hepatic encephalopathy found that survival was longest in patients receiving which secondary prophylactic agent(s)?

a. Lactulose monotherapy

b. Rifaximin monotherapy

c. Lactulose/rifaximin combination therapy

d. Probiotic monotherapy

5. A retrospective review of claim data found that the percentage of patients that actually received secondary prophylactic therapy for overt hepatic encephalopathy in 2011 was:

a. <16%

b. 36%

c. 56%

d. >76%

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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.

	This learning objective did (or will) increase/improve my:	*High Impact*	*Moderate Impact*	*No Impact*	*Not Applicable*
• Assess emerging new therapies for the treatment of acute overt hepatic encephalopathy and as secondary prophylactic agents for the prevention of recurrence of overt hepatic encephalopathy	***Knowledge***	❑	❑	❑	❑
	Competence	❑	❑	❑	❑
	Performance	❑	❑	❑	❑
	Patient Outcomes	❑	❑	❑	❑
• Evaluate long-term rifaximin efficacy and safety data as secondary prophylactic therapy for overt hepatic encephalopathy	***Knowledge***	❑	❑	❑	❑
	Competence	❑	❑	❑	❑
	Performance	❑	❑	❑	❑
	Patient Outcomes	❑	❑	❑	❑
• Describe survival probability of patients who have experienced overt hepatic encephalopathy and how choice of secondary prophylactic treatment may affect survival probability	***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
❑ Practice-based learning and improvement
❑ Interpersonal and communication skills
❑ Employ evidence-based practice
❑ Interdisciplinary teams
❑ Professionalism
❑ Quality improvement
❑ Medical knowledge
❑ System-based practice
❑ Utilize informatics
❑ None of the above

- 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 *(select all that apply)*?

❑ 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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REQUEST FOR CREDIT

If you wish to receive acknowledgement of participation for this activity, please fill in your contact information and fax back pages 7-10 to (973) 939-8533.

Please do not use abbreviations.
We need current and complete information to assure delivery of participation acknowledgement.

Degree *(please mark appropriate box and circle appropriate degree)*

❑ MD/DO ❑ PharmD/RPh ❑ NP/PA ❑ RN ❑ Other _____

Full Name *(please print clearly)*
Last Name: First Name: Middle Initial:

Street Address:

City: State or Province: Postal Code:

Phone: – – Ext. Fax: – –

Specialty:

E-mail Address:

Signature is required to receive statement of credit

Signature: _____ Date: _____

Attestation to time spent on activity is required

Purdue University College of Pharmacy designates this enduring material for a maximum of *1 AMA PRA Category 1 Credit(s)*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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