Comparative Effects of Available Thiazolidinediones: A Review of the Literature

Scott W. Yates, MD, MBA

Abstract

Diabetes has reached epidemic proportions in the U.S.; it is projected to become one of the leading causes of death and disability, and it already represents the largest single economic disease burden in our society. It is estimated that diabetes will ultimately affect one third of individuals who were born in the U.S. in the year 2000. Treatment regimens for type-2 (non–insulin-dependent) diabetes must address control of both blood glucose and blood lipid levels. There appear to be significant differences in the nonglycemic (particularly the lipid) effects of two thiazolidinedione medications (pioglitazone and rosiglitazone), currently marketed in the U.S.

Two types of evaluations have been used to examine the differences in the glycemic and nonglycemic clinical effects of these two agents: (1) prospectively, after discontinuation of troglitazone therapy, and (2) retrospectively, with chart reviews.

There are no consistent findings with respect to improvement or degradation of glycemic control, or change in body weight, following switches from troglitazone to rosiglitazone, or from troglitazone to pioglitazone, but lipid levels are affected. In patients who previously received troglitazone, rosiglitazone tended to increase total cholesterol (TC) and triglyceride levels, and pioglitazone tended to decrease TC, low-density lipoprotein cholesterol (LDL-C), and triglycerides and to increase high-density lipoprotein-cholesterol (HDL-C).

From the clinical chart reviews, we can draw three conclusions. First, it appears that there are no significant differences in glycohemoglobin (HbA1c) reductions between these medications. Second, rosiglitazone seems to increase both TC and LDL-C levels. Third, pioglitazone decreases TC and triglycerides and increases HDL-C levels.

These findings may be significant in the management of type-2 diabetes. Prevention of cardiovascular morbidity and mortality is of the utmost importance in this population. If dyslipidemia is worsened by efforts to control hyperglycemia, some of the benefit of treatment may be lost.

Introduction

An epidemic of diabetes is raging in the U.S. Twelve million people have a confirmed diagnosis of diabetes, and almost five million people have the disease but are unaware that they have it. It is projected that one of every three individuals who were born in the U.S. in the year 2000 will eventually have diabetes.¹

In 2002, $92 billion worth of health care expenditures were devoted to the direct care of patients with diabetes. Combined with the cost of its complications, diabetes represents the largest single economic disease burden on our society.²

Type-2 (non–insulin-dependent) diabetes mellitus is characterized by decreased sensitivity to insulin action in muscle, liver, and fat cells as well as by a progressive decline in pancreatic insulin production. The precise causes of insulin resistance and eventual failure of the beta cells remain unclear, but both genetic predisposition and environmental factors may interact.³⁻⁵ In particular, obesity and a sedentary lifestyle are closely linked to the development of type-2 diabetes.⁶⁻⁷

The Thiazolidinediones

Troglitazone, the first clinically useful drug in the thiazolidinedione class, was approved for sale in 1997.⁸ Thiazolidinediones lower blood glucose and insulin levels and may preserve or improve beta cell function.⁹⁻¹¹ On March 21, 2000, Parke-Davis withdrew troglitazone (Rezulin®) from the U.S. market because of its association with hepatotoxicity. Two additional members of the thiazolidinedione class were introduced in the U.S. in 1999: rosiglitazone (Avandia®, GlaxoSmithKline) and pioglitazone (Actos®, Takeda). Some meta-analyses have not found any evidence of risk of hepatotoxicity with the newer agents.¹²⁻¹³

Thiazolidinediones exert their clinical effects, at least in part, through modulation of the nuclear peroxisome proliferator-activated receptor (PPAR). PPARs can also be activated by...
fatty acids or their derivatives. They are transcription activators, and ligand binding regulates their action.14

Cardiovascular disease is the leading cause of morbidity and mortality in patients with diabetes. Hyperinsulinemia (a marker of insulin resistance) is an independent risk factor for cardiovascular disease.15 Diabetes treatments that decrease hyperinsulinemia and insulin resistance seem to be more protective against cardiovascular events than those that do not have an effect on these factors.16 Because the available thiazolidinediones lower blood sugar, improve both hyperinsulinemia and insulin resistance, and affect lipid levels, much interest has been focused on these drugs for their potential benefits in decreasing cardiovascular risk.

Rosiglitazone and pioglitazone are indicated for the treatment of type-2 diabetes. There have been no published head-to-head, randomized, blinded clinical trials comparing these two drugs. This article reviews the literature from comparison studies evaluating the various effects of these drugs on glucose control, lipids, and body weight. Studies to date can be divided into two categories for consideration:

• “Troglitazone switch studies.” Many patients who had been previously treated with troglitazone were switched to either rosiglitazone or pioglitazone. Five studies of this type will be discussed.
• Studies resulting from retrospective medical record analyses. Four of these studies will be discussed.

Troglitazone Switch Studies

With the removal of troglitazone from the market, several investigators collected data on patients who were switched to either rosiglitazone or pioglitazone. Changes in glycemic control and lipid parameters are reported in Table 1A and B; some studies have reported changes in body weight as well.

Gegick and Altheimer17

The authors observed 163 patients after a switch from troglitazone to either pioglitazone or rosiglitazone in a nonrandomized study. Of the total number of patients who followed, 144 were evaluated for changes in glycemic control and 125 were assessed for alterations in lipid control. After an observation period averaging 3.2 months, the changes in glycemic control were similar; changes in weight were not significant (see Table 1A).

Although total cholesterol (TC), triglycerides (TG), and low-density lipoprotein-cholesterol (LDL-C) levels decreased in the pioglitazone group, these same values increased in the rosiglitazone group. The endpoint values for high-density lipoprotein-cholesterol (HDL-C) also differed: they were elevated in the pioglitazone group and lowered in the rosiglitazone group (see Table 1B).

Davidson et al.18

The investigators randomly switched 39 patients from troglitazone to maximum doses of either pioglitazone or rosiglitazone. Even though the study was small, significant differences were seen in the effects of these agents on glycemic control, TC, and HDL-C levels (see Table 1A and B).

Faiman et al.19

Faiman et al. prospectively randomly assigned 58 subjects to either pioglitazone or rosiglitazone following troglitazone therapy. Two or more months after the switch, glycemic control and lipid control were assessed. No significant differences were observed between the groups for any measured value except for TG levels. Data from this trial are included in Table 1A and B.

Khan et al.20

In this study, 186 patients were switched in a random fashion to either pioglitazone or rosiglitazone after a two-week washout period. Of these patients, 127 completed follow-up. There were no significant differences in the populations in terms of sex, age, weight, TC, HDL-C, LDL-C, TG, or hemoglobin (HbA1c) at the time of randomization. At four months’ follow-up, no differences between the groups were found with regard to glycemic control.

Significant weight gain (approximately 2 kg) was seen in both groups (see Table 1A). Subjects in the pioglitazone group had decreased TC and HDL-C concentrations, whereas the rosiglitazone group showed no significant lipid changes. Numerical data from this study are estimated (but are not included) from graphs in the Khan manuscript (see Table 1B).

Rosenblatt et al.21

Rosenblatt et al. randomly switched 99 subjects from troglitazone to either pioglitazone or rosiglitazone. Baseline lipid and glycohemoglobin values were obtained and compared with those during an 18-month follow-up period. The researchers observed no differences in the rate of development of edema, no significant changes in weight or hematocrit, and no elevations of liver function values. Both groups of patients tended to undergo a loss of glycemic control over time (see Table 1A). The only significant differences noted in lipid values were a decrease in TG in the pioglitazone patients (see Table 1B).

Summary

There are no consistent findings in the studies reviewed with respect to improvement or degradation of glycemic control, or change in weight, following switches from troglitazone to rosiglitazone or to pioglitazone. The number of subjects in the randomized trials was small, and the subjects in the Gegick study were not randomly assigned to treatment groups.17 With these limitations in mind, the switching therapies did appear to have different effects on lipid levels: rosiglitazone tended to increase TC and TG concentrations, and pioglitazone tended to decrease TC, LDL-C, and TG levels and to increase HDL-C levels.

Retrospective Chart Reviews

Physicians, payers, patients, and pharmaceutical companies are very interested in clarification of the apparent differences between rosiglitazone and pioglitazone. To this end, at least five studies have been performed in large populations of patients—as retrospective chart reviews or, in one instance, as a pharmaceutical claims database survey.
In 2000, King documented the characteristics of a total of 101 patients followed in his practice who took troglitazone, pioglitazone, or rosiglitazone. Rosiglitazone increased TG and LDL-C levels, whereas pioglitazone decreased TG and increased HDL-C levels. There appeared to be a similar effect on glycemic control but more edema with pioglitazone. Unfortunately, statistical analyses are not reported for this trial, and the trial data are not included in Table 2A and B; however, the data presented are consistent with those found by other investigators.

Hutcheson et al. Hutchens et al. analyzed the drug-use patterns of 5,773 patients who began treatment with either pioglitazone or rosiglitazone. These patients were able to be followed in their pharmacy claims database for the next six months. Initiation or upward titration of statin therapy was used as a surrogate for the lipid effects of the thiazolidinedione therapy. Because no laboratory data were available in their database, lipid and glycemic levels are not presented. Fewer pioglitazone patients than rosiglitazone patients added their dose of antihyperlipidemic agents (12.8% vs. 16.4%, \( P < .001 \)) or increased it (5.1% vs. 8.4%, \( P = .004 \)) during the study period.

Boyle et al. The largest trial of this type to date, by Boyle et al. in 2002, is a retrospective study that included 1,115 patient records from 605 primary care practices in the U.S. Baseline demographics did not differ between the rosiglitazone and pioglitazone groups of patients, but baseline HDL-C levels were lower in the pioglitazone group. Most of the patients (915) received combination therapy consisting of either rosiglitazone or pioglitazone and metformin and/or a sulfonylurea. Reductions in glucose levels were similar, but pioglitazone treatment resulted in a reduction in TC, TG, LDL-C levels and an increase in HDL-C levels. Rosiglitazone therapy resulted in a reduction of TG and HDL-C and an increase in TC and LDL-C levels (Table 2A and B).

### Table 1 Troglitazone Switch Studies

#### 1A Changes in Glycemic Values and Weight

<table>
<thead>
<tr>
<th>No. (Total)</th>
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<td>Gegick, 2001</td>
<td>163</td>
<td>NS</td>
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<td>Davidson, 2001</td>
<td>39</td>
<td>NS</td>
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<td>NS</td>
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<td>Faiman, 2001</td>
<td>58</td>
<td>+1.18%4</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Rosenblatt, 2002</td>
<td>99</td>
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#### 1B Changes in Lipid Values

<table>
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<th>No. (Total)</th>
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<th>HDL-C</th>
<th>LDL-C</th>
<th>TG</th>
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<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td>Gegick, 2001</td>
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<td>+15 mg/dl1,8</td>
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<tr>
<td>Davidson, 2001</td>
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<td>+16 mg/dl1</td>
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<td>NS</td>
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<tr>
<td>Faiman, 2001</td>
<td>58</td>
<td>NS</td>
<td>NS</td>
<td>+44 mg/dl3</td>
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<td>Rosenblatt, 2002</td>
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#### Troglitazone Switch Studies

<table>
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<th>HDL-C</th>
<th>LDL-C</th>
<th>TG</th>
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<tr>
<td>Rosenblatt, 2002</td>
<td>99</td>
<td>NS</td>
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</table>

1 \( P < .05 \) from baseline.
2 \( P < .01 \) from baseline.
3 \( P = .014 \) for difference between ROSI and PIO.
4 \( P < .0001 \) from baseline.
5 \( P < .001 \) from baseline.
6 \( P = .0017 \) from baseline.
7 \( P < .01 \) for difference between ROSI and PIO.
8 \( P < .05 \) for difference between ROSE and PIO.
9 \( P = .0031 \) from baseline.

HbA1c = glycosylated hemoglobin; HDL = high-density lipoprotein-cholesterol; LDL = low-density lipoprotein-cholesterol; NS = not significant (\( P > .05 \)); PIO = pioglitazone; ROSI = rosiglitazone; TC = total cholesterol; TG = triglycerides.
Summary

The available data are limited to the studies reviewed in this article. Because there might be significant differences in the lipid effects of these medications, additional investigation is needed.

Discussion

The most common cause of morbidity and mortality in patients with diabetes mellitus is cardiovascular disease; acute myocardial infarction is the most common cause of death. Elevated LDL-C concentrations, low HDL-C concentrations, and high glycohemoglobin levels were found to be the best prognostic indicators of a coronary event in the United Kingdom Prospective Diabetes Study (UKPDS). Elevated TG levels have been shown to increase the risk for cardiovascular events in type-2 diabetic patients in several studies.

The troglitazone switch studies described here serve to confirm and reinforce the conclusions that can be drawn from the retrospective chart reviews. Changes in glycemic control appeared to be similar with rosiglitazone and pioglitazone, but there were differences in the effects of these drugs on blood lipid levels. Rosiglitazone tended to increase TC and LDL-C levels, whereas pioglitazone tended to decrease TC and TG and to increase HDL-C without a significant change in LDL-C. These lipid effects appeared to be of small magnitude, and a shift in LDL-C particle size might be responsible for some of the LDL elevation seen with rosiglitazone. Further study is needed to clarify these lipid effects and to examine their impact on clinical outcomes.

The elevated cardiovascular risk seen in patients with type-2 diabetes was the impetus for recommendations from both the American Diabetes Association and the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults to aggressively lower elevated cholesterol levels in adult diabetics, with an LDL-C targeted goal of less than 100 mg/dl, a TG level below 150 mg/dl, and an HDL-C level greater than 40 mg/dl.

Conclusion

If the changes exerted on lipid levels were confirmed in a randomized, prospective fashion, they would be cause for significant concern among physicians who provide care for patients with type-2 diabetes. Additional retrospective and prospective studies are needed. It is hoped that research with PPARs will lead to the development of agents that act as agonists of both PPAR gamma and PPAR alpha. Stimulation of both PPARs may result in beneficial effects on both glycemic and lipid parameters.

References


Table 2  Retrospective Review Studies

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<th>Rosiglitazone Patients</th>
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<tr>
<td></td>
<td>HbA1c</td>
<td>Weight</td>
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<td></td>
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<tr>
<td>No. (Total)</td>
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<td>–1.18%</td>
</tr>
<tr>
<td></td>
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<td>–1.1%</td>
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<tr>
<td>Peters Harmel, 2004</td>
<td>829</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>TC</td>
<td>HDL</td>
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<td>Boyle, 2002</td>
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<tr>
<td>No. (Total)</td>
<td>1,115</td>
<td>+5 mg/dl</td>
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<tr>
<td>Peters Harmel, 2004</td>
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<td>+8 mg/dl</td>
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<tr>
<td>1 P = .041 from baseline.</td>
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<tr>
<td>2 P &lt; .001 from baseline.</td>
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<tr>
<td>3 P = .030 from baseline.</td>
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<td>4 P = .002 for difference between ROSI and PIO.</td>
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<td>5 P = .003 for difference between ROSI and PIO.</td>
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<td>6 P = .001 from baseline.</td>
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<tr>
<td>7 P = .03 for difference between ROSI and PIO.</td>
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</table>

HbA1c = glycosylated hemoglobin; HDL = high-density lipoprotein-cholesterol; LDL = low-density lipoprotein-cholesterol; NS = not significant (P > .05); PIO = pioglitazone; ROSI = rosiglitazone; TC = total cholesterol; TG = triglycerides.


Disclosure
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Expiration Date: September 30, 2005

**TOPIC:** Comparative Effects of Available Thiazolidinediones: A Review of the Literature

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Multiple Choice
Select the one correct answer.

1. Regarding diabetes, which of the following statements is incorrect?
   a. Diabetes represents the largest single economic disease burden on our society.
   b. It is projected that one of every three individuals born in the U.S. in the year 2000 will develop diabetes during their lifetime.
   c. A sedentary lifestyle is the only factor linked to the development of type-2 diabetes mellitus.
   d. Type-2 diabetes is characterized by decreased sensitivity to insulin action in muscle, liver, and fat cells.

2. Which of the following is incorrect with regard to the thiazolidinedione class of drugs?
   a. Thiazolidinediones act to lower blood glucose and insulin levels and may preserve or improve beta-cell function.
   b. Thiazolidinediones exert their clinical effects, at least in part, through modulation of the nuclear peroxisome proliferator-activated receptor (PPAR).
   c. Recent meta-analyses of trials using pioglitazone or rosiglitazone have not found any evidence of risk of hepatotoxicity with the newer agents.
   d. Three thiazolidinediones are currently marketed in the U.S.

3. According to the current literature, which of the following statements is true?
   a. Diabetes treatments that decrease hyperinsulinemia and insulin resistance seem to be more protective against cardiovascular events than those that do not have an impact on these factors.
   b. Because thiazolidinediones lower blood sugar levels, improve both hyperinsulinemia and insulin resistance, and affect lipid levels, they may have a potential benefit in decreasing cardiovascular risk.
   c. Hyperinsulinemia is an independent risk factor for cardiovascular disease.
   d. All of the above

4. Studies that examined patients who were switched from troglitazone to either pioglitazone or rosiglitazone found that:
   a. Glycemic control was better for patients who were switched to pioglitazone.
   b. Glycemic control was better for patients who were switched to rosiglitazone.
   c. No clear inferences could be made about glycemic control.
   d. All patients who were switched from troglitazone experienced better glycemic control.

5. Which of the following is true concerning the study by Khan et al. regarding patients switched from troglitazone to either pioglitazone or rosiglitazone?
   a. Patients in the pioglitazone group exhibited better glycemic control.
   b. Patients in the pioglitazone group exhibited significantly more weight gain.
   c. Patients in the pioglitazone group exhibited significantly increased triglyceride levels.
   d. Patients in the pioglitazone group exhibited significantly decreased total cholesterol levels.

6. Which of the following is true in the study by Rosenblatt et al. regarding patients switched from troglitazone to either pioglitazone or rosiglitazone?
   a. Patients in the pioglitazone group exhibited better glycemic control.
   b. Patients in the pioglitazone group exhibited significantly more weight gain.
   c. Patients in the pioglitazone group exhibited significantly decreased triglyceride concentrations.
   d. Patients in the pioglitazone group exhibited significantly decreased total cholesterol levels.

7. Which of the following statements is true based on the article by King et al.?
   a. Rosiglitazone decreased triglycerides and HDL-C levels.
   b. Edema was more common with rosiglitazone.
   c. Triglycerides and LDL-C increased with rosiglitazone.
   d. Rosiglitazone was determined to have improved control of hyperglycemia.

8. Which of the following statements is false according to the study by Hutchins et al.?
   a. Patients were followed in the pharmacy claims database for six months.
   b. An increase in LDL-C was used as a marker for lipid effects of thiazolidinediones.
   c. Fewer patients in the pioglitazone group increased their dose of antihyperlipidemic agents.
   d. Initiation or up-titration of statin therapy was used as a marker for lipid effects of the thiazolidinediones.

9. According to the article published by Boyle and colleagues, all of the following statements are true except:
   a. This was a retrospective study.
   b. Baseline HDL-C levels were lower in the pioglitazone group.
   c. Patients were treated with combinations using either pioglitazone or rosiglitazone and metformin and/or glucose.
   d. Treatment with pioglitazone resulted in decreased triglyceride, total cholesterol, and LDL-C levels and increased HDL-C levels.

10. In the study conducted by Peters Harmel and associates, all of the following statements are true except:
    a. The researchers focused on endocrinology practices all over the U.S.
    b. They reviewed records of patients who were taking combination medications such as either metformin and pioglitazone or metformin and rosiglitazone.
    c. Patient demographics were similar at the baseline examination.
    d. Patients taking metformin and pioglitazone experienced significant increases in triglyceride and LDL-C levels.
CE Registration and Evaluation Form

Date of publication: September 2004
Title: Comparative Effects of Available Thiazolidinediones: A Review of the Literature
Authors: Scott W. Yates, MD, MBA
Submission deadline: September 30, 2005
ACPE Program # 079-999-04-021-H01

Registration

Name: ____________________________________________________________ Degree: ____________________________________
Street address: ______________________________________________ Last 4 Digits of Social Security No. (Web ID): __________
City: ___________________________________  State: _________  Zip:__________  Telephone: _____________________________
E-mail Address: _____________________________________ Check one: □ Physician □ Pharmacist □ Other
Time needed to complete this CE activity in hours: □ 0.5 hr □ 1 hr □ 1.5 hr □ 2 hr □ Other ________________

Certification: I attest to having completed this CE activity. ___________________________________________________________
Signature (required) Date _______________

Answer Sheet

Please fill in the box next to the letter corresponding to the correct answer

1. a □ b □ c □ d □ 6. a □ b □ c □ d □
   2. a □ b □ c □ d □ 7. a □ b □ c □ d □
   3. a □ b □ c □ d □ 8. a □ b □ c □ d □
   4. a □ b □ c □ d □ 9. a □ b □ c □ d □
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Evaluation

Rate the extent to which:

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<td>1. Objectives of this activity were met</td>
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<td>2. You were satisfied with the overall quality of this activity</td>
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<td>3. Content was relevant to your practice needs</td>
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<td>4. Participation in this activity changed your knowledge/attitudes</td>
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<td>5. You will make a change in your practice as a result of participation in this activity</td>
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<td>6. This activity presented scientifically rigorous, unbiased, and balanced information</td>
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<td>7. Individual presentations were free of commercial bias</td>
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<td>8. Adequate time was available for Q&amp;A</td>
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<td>9. Which ONE of the following best describes the impact of this activity on your performance:</td>
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<td>10. Will you take any of the following actions as a result of participating in this educational activity (check all that apply)</td>
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<td>□ Discuss new information with other professionals</td>
<td>□ Consult the literature</td>
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<td>□ Discuss with industry representative(s)</td>
<td>□ Participate in another educational activity</td>
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<td>□ Other _________________________</td>
<td>□ None</td>
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</table>

Send the completed form and $10 payment (make checks payable to P&T) to: Department of Health Policy, Thomas Jefferson University, Attn: Continuing Education Credit, 1015 Walnut Street, Suite 115, Philadelphia, PA 19107.