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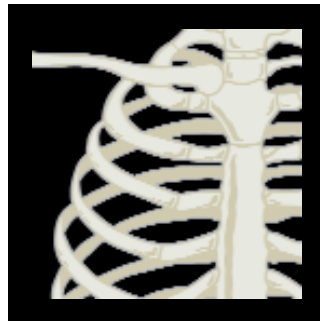
# OSTEOPOROSIS: THE ERA OF THE BISPHOSPHONATES

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## P A R T T H R E E

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## Statement of Educational Need

This activity is designed to respond to the needs of endocrinologists and other physicians who care for women at risk for osteoporosis or with established osteoporosis.

## Educational Objectives

After listening to the CD, reading this monograph, and completing the post-test, the participant should be able to:

- Describe results of important recent studies of osteoporosis
- Better understand the implications of the Women's Health Initiative study
- Describe available diagnostic guidelines and techniques
- Describe the modes of action of the agents currently used to treat osteoporosis
- Have a better understanding of data regarding the relative effectiveness of the various agents used to treat osteoporosis
- Choose the appropriate treatment modalities for patients newly diagnosed with osteoporosis

## Statement of Educational Method

The educational information is presented in an eight-page monograph and a 25-minute audio CD.

## Statement of Evaluation Instrument

A 10-question, multiple-choice post-test is used as the evaluation instrument. An activity evaluation questionnaire will be completed by each participant.

## Statement of Intended, or Target, Audience

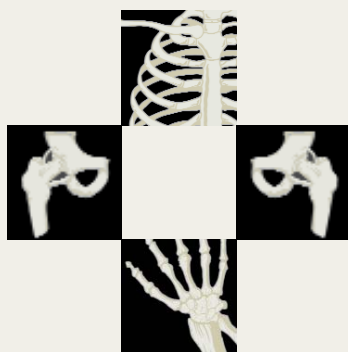
This activity is intended for, but not limited to: endocrinologists, and other physicians who care for patients with with osteoporosis or who are at risk for osteoporosis.

## Instructions

To earn 1 hour of category 1 credit, listen to the CD and read the material in this monograph carefully. Complete the activity evaluation and answer the post-test questions on the accompanying questionnaire. Send the questionnaire in the enclosed envelope to: CPDE REGISTRAR, P.O. Box 980048, Richmond, VA 23298-0048. ATTN: OSTEO PROGRAM, PART 3. Your credit certificate will be returned. Participation is confidential. Estimated program completion time: 1 hour.

Activity Number: END IN 09 101 04  
Release date: 09-30-04. Expiration date: 08-31-06.

Supported by an unrestricted educational grant from Merck & Co., Inc.



Clinicians who treat women in their perimenopausal and postmenopausal years increasingly find that prevention and management strategies for osteoporosis are a topic of uncertainty and controversy. Although the long-anticipated Women's Health Initiative study showed a clear benefit for osteoporosis prevention from long-term hormone therapy (HT) [Rossouw 2002], disturbing data about increased cardiovascular, cerebrovascular [Kuller 2003], and cancer risks [Antoine 2004] associated with HT continue to appear. These developments have increased the reluctance of many physicians and patients to continue or initiate HT and decreased preventive therapy options for many patients at risk of osteoporosis.

## INTRODUCTION



The aging of the United States population has increased the number of women who reach perimenopause or menopause each year and also intensified the urgency for effective prevention and treatment of osteoporosis. However, recent studies have shown that underdiagnosis of low BMD and osteoporosis is common and the optimum use of screening methods, non-pharmacological strategies, and pharmacological therapies is complex and not fully resolved.

Recent developments in the field of osteoporosis also include new results from clinical trials that show risks and benefits of long-term drug therapy for women with osteoporosis. This monograph will review current events in the field of osteoporosis and discuss current treatment strategies in light of these events.



## RECENT DEVELOPMENTS AFFECTING TREATMENT OF OSTEOPOROSIS

As expected, initial and continuing results from the WHI showed that HT significantly increased bone mineral density (BMD) and reduced the risk of fracture compared to placebo. [Cauley 2003] However, data that began to appear from the estrogen/progestin arm of the WHI in 2002 also showed an increased risk of breast cancer and stroke, with little or no cardiovascular benefit from long-term HT. [Chlebowski 2003; Wassertheil-Smoller 2003; Manson 2003] With the exception of increased breast cancer risk, these results were recently confirmed in the estrogen-alone arm of the study [Anderson 2004], which also suggested increased risk of dementia and cognitive impairment associated with HT in a subgroup of women over age 65. [Shumaker 2004; Espeland 2004]

### ◀ THE WOMEN'S HEALTH INITIATIVE STUDY RESULTS

Because of these developments, many postmenopausal women in the United States discontinued HT or continued with much lower doses of HT for shorter periods of time. [Ettinger 2003] Both accelerated and normal rates of bone loss were documented in cohorts of patients after discontinuation. [Gallagher 2002] After 5 years, the risk of hip fracture in women who had discontinued HT was the same as in women who had never received HT. In another study, the risk of hip fracture during the first 5 years after discontinuation was as high or higher in women who had discontinued HT as in women who had never received HT. [Yates 2004]

Although many physicians and patients are reluctant to rule out HT altogether, these results have provoked discussion about alternative prevention measures for women who have discontinued HT or will use it for limited periods.

Another current issue in osteoporosis is low rates of BMD screening and diagnosis of osteoporosis in postmenopausal women. A recent alarming study of patients who had already suffered vertebral compression fractures showed that only 38%, including 46% of women and 19% of men, had received a diagnosis of osteoporosis before the fracture, and only 69% of the women who had been diagnosed were receiving osteoporosis prescription medications. [Neuner 2003]

### ◀ THE DILEMMA OF DIAGNOSIS

**NEW QUESTIONS FOR TREATMENT**

In view of increased awareness of the need for close monitoring of BMD in postmenopausal women who may have discontinued HT or changed to low doses of HT, the National Osteoporosis Foundation recently revised its guidelines for determining who should be treated. Hip and spine dual-energy x-ray absorptiometry should be used to measure BMD. The number of standard deviations from the average BMD of young adults is the T-score. In addition, the contribution of risk factors, such as history of fractures, a family history of osteoporotic fractures, smoking, a thin build, and frequent falls, is evaluated for each patient. Patients with BMD T-scores less than -2.0 and no other risk factors, patients with BMD T-scores below -1.5 and one or more other risk factors, and patients who have had a prior vertebral or hip fracture should receive osteoporosis therapy.[NOF 2004]

The role of high bone turnover as a risk factor for fractures is another issue that has not been resolved. Testing of serum and urine markers of bone turnover is not routine in primary care, but may be considered when women are discontinuing estrogen therapy or rapid bone loss is suspected. Some evidence suggests that changes in markers of bone turnover may predict fracture risk as well as, or better than, changes in BMD.[Sarkar 2004]

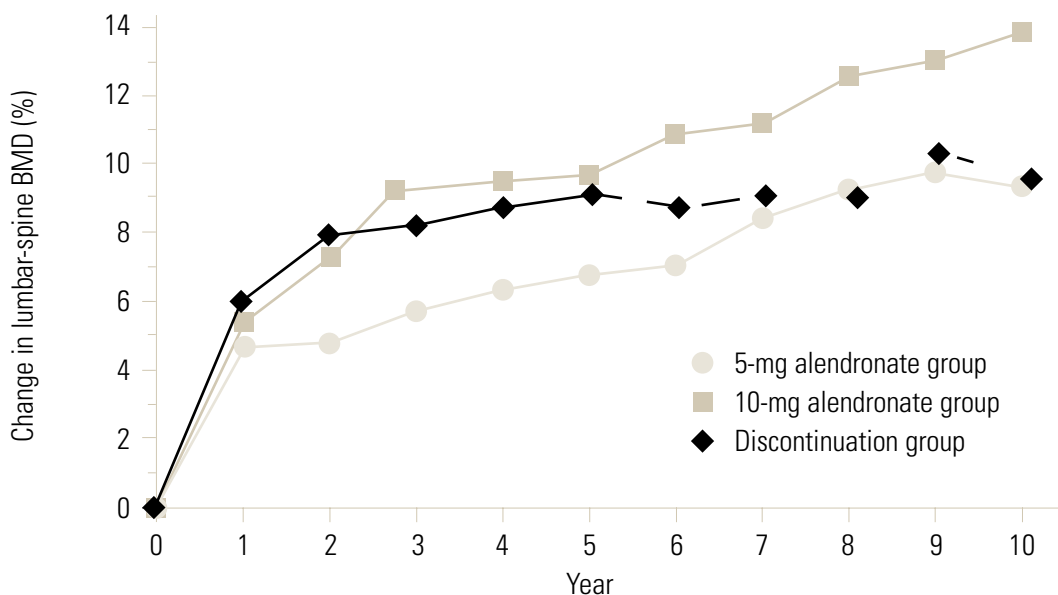
**NEW CLINICAL TRIAL RESULTS FOR ALENDRONATE (FOSAMAX®)**

Alendronate has been available in the United States since 1995 and is associated with the most extensive clinical experience of any non-hormonal therapy for prevention of osteoporosis. A recent publication in the *New England Journal of Medicine* [Bone 2004] reports results for 247 postmenopausal women with osteoporosis who received alendronate for up to 10 years in a randomized, double-blind, placebo-controlled study.

In patients who received 5 mg/d or 10 mg/d alendronate for up to 10 years, BMD at the lumbar spine continued to increase during years 6 through 10 and years 8 through 10 (Figure 1). The alendronate groups had no decreases in BMD at any skeletal site during years 6 through 10. Markers of bone remodeling were reduced to low levels that were stable throughout the study. In patients who discontinued active treatment and began to receive placebo after 5 years, decreases in BMD occurred at several sites but remained above baseline at the 10-year follow-up measurement. Also, bone markers increased in patients who discontinued active treatment but remained below baseline measurements.[Bone 2004]

**FIGURE 1**

Ten-year alendronate study: change in lumbar-spine BMD (%)



## After 5 years, the risk of hip fracture in women who had discontinued HT was the same as in women who had never received HT.

Patients who received alendronate during the study had lower rates of loss of height and lower rates of vertebral fracture compared with patients who discontinued treatment. Safety profiles were similar in treatment and placebo groups.[Bone 2004]

Preliminary results are also available from a year-long study (the Efficacy of Fosamax® vs Evista® Comparison Trial, or EFFECT) that compared increases in BMD in 456 women with osteoporosis. The patients were randomized to receive alendronate 70 mg once weekly or raloxifene 60 mg per day and BMD was measured at baseline, after 6 months of treatment, and after 12 months of treatment. The primary end point was percent change in BMD at the lumbar spine at the one-year time point.[Luckey 2004]

After one year, increases in lumbar-spine BMD in patients who received alendronate were more than 2-fold higher than increases in patients who received raloxifene (4.4% vs 1.9%;  $p < 0.001$ ). Total hip BMD increased 2.0% for patients who received alendronate and 1.0% for patients who received raloxifene at the one-year time point ( $p < 0.001$ ). The response rate, defined as the percentage of patients who increased or maintained BMD, was 94% for the alendronate group and 75% for the raloxifene group.[Kagan 2003] There were no clinically apparent vertebral or hip fractures in either treatment arm. These data were presented at the 51st Annual Meeting of the American College of Obstetricians and Gynecologists.[Kagan 2003]



### MECHANISM OF ACTION AND EFFICACY EVALUATIONS OF NON-ESTROGEN OSTEOPOROSIS THERAPIES

The goal of osteoporosis therapy is to promote increases in BMD and reductions in the risk of osteoporotic fracture. However, as previously mentioned, markers of bone turnover are increasingly used to indicate bone quality and fracture risk. BMD maintenance and bone quality is the result of balance between the bone synthesis activities of osteoblasts with the bone resorption activities of osteoclasts. Estrogen is an important modulator of bone in premenopausal women and works primarily through inhibiting resorption.[Hardman 1996]

Estrogen therapy is now recommended, in low doses and for short periods of time, only for treatment of urogenital or vasomotor symptoms in peri- or postmenopausal women. [ACOG 2003] However, ultra-low-dose formulations of estrogen are under investigation, and one of these was recently approved for the prevention of osteoporosis in postmenopausal women (Menostar®; Berlex). *Ettinger et al* conducted a placebo-controlled, double-blind trial of very-low-dose transdermal estradiol (0.014 mg/d) in 417 women aged 60-80, with bone mineral density z-scores of -2.0 or higher.[Ettinger 2004] Median plasma estradiol levels in the treated group (n=208) increased from 4.8 pg/mL at baseline to 8.5 pg/mL at one year and 8.6 pg/mL at two years ( $p < 0.001$ ). Lumbar-spine bone mineral density increased 2.6% in the estradiol group and 0.6% in the placebo group (between-group difference 2.0%,  $p < 0.001$ ). Mean total hip bone mineral density increased 0.4% in the estradiol group and decreased 0.8% in the placebo group (between-group difference 1.2%,  $p < 0.001$ ).

Several classes of therapy are now used in the place of estrogen for prevention and treatment of osteoporosis. These therapies work through inhibiting resorption and by anabolic mechanisms.

**ANTIRESORPTIVE THERAPIES**



**SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS)**

SERMS include tamoxifen, indicated for adjuvant therapy to reduce the risk of breast cancer, and raloxifene (Evista®; Lilly). Raloxifene is the only SERM indicated to prevent or treat osteoporosis. Raloxifene is a non-hormonal agent that binds selectively to estrogen receptors on many cells, producing activation of some estrogen pathways and blockage of others. Raloxifene interactions with the estrogen receptor inhibit bone resorption. Raloxifene does not have estrogen-like adverse effects on endometrial and breast tissue.[Evista PI]

The efficacy of raloxifene for prevention and treatment of osteoporosis was shown in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial.[Ettinger 1999] Raloxifene treatment was associated with modest effects on bone density and was shown to produce reductions in bone turnover markers. In addition, the risk of vertebral fractures was reduced. There were no data for nonvertebral fractures from this trial. The MORE trial also showed that raloxifene treatment produced significant reductions in the incidence of breast cancer as well as cardiovascular and cerebrovascular disease.[Ettinger 1999]

**CALCITONIN**

Calcitonin (Miacalcin®; Novartis) is a polypeptide hormone secreted by the thyroid gland. It interacts directly with receptors on osteoclasts, inhibiting bone resorption.[Hardman 1996] There are two dosage forms of salmon calcitonin, injectable (rarely used) and a nasal spray. The nasal spray form was evaluated in the Prevent Recurrence of Osteoporotic Fractures (PROOF) trial. In this large, double-blind, randomized, placebo-controlled trial, postmenopausal women with established osteoporosis received 100, 200, or 400 IU calcitonin daily by nasal spray. Lumbar-spine BMD was increased and markers of bone turnover were decreased in all treatment groups compared with placebo ( $p < 0.01$  for all comparisons). In this study, 200 IU per day significantly reduced the risk of new vertebral fractures by 33% overall and by 36% in patients with existing vertebral fractures. However, 100 IU and 400 IU per day reductions in fractures did not reach significance.[Chesnut 2000]

Results from this trial are problematic, due to the dropout of 59% of the patients before the end of the trial and the lack of dose response in fracture reduction. In addition, the PROOF study was only partially blinded, because physicians and patients were aware of BMD measurements as the trial progressed.

**BISPHOSPHONATES**

Bisphosphonates are synthetic analogues of pyrophosphate that work by binding preferentially to hydroxyapatite in bone where active bone resorption is taking place under osteoclasts. Bone resorption is inhibited at the sites where bisphosphonates are bound and bone formation continues, resulting in net increases in bone mass at those sites.[Fosamax PI] Two bisphosphonates are indicated for osteoporosis prevention and treatment in the United States, alendronate (Fosamax®; Merck & Co.) and risedronate (Actonel®; Procter & Gamble). To maximize absorption of bisphosphonates, they must be taken on an empty stomach first thing in the morning with water only, and cannot be followed by any food or drink for at least 30 minutes.[Fosamax PI]

Alendronate is the most potent available agent for prevention and treatment of osteoporosis. It was studied in the Fracture Intervention Trial (FIT), a large, randomized, double-blind, placebo-controlled study in patients with low BMD measurements. Patients who received alendronate (5 mg/day, increased to 10 mg/day two years into the study) had increases in BMD (average 7% to 9% at the spine and 5% to 8% at the hip compared to placebo). By year 4, the risk of fracture in women with osteoporosis but no prior hip fractures was reduced by 56%.[Black 2000] A meta-analysis of five studies of alendronate in postmenopausal women showed an approximately 50% reduction in risk for hip fractures.[Karpf 1997]

Alendronate has recently become available in weekly formulations that are equivalent in efficacy to daily formulations and may be associated with fewer esophageal and gastrointestinal side effects. [Schnitzer 2000; Luckey 2003]

Risedronate produces moderate effects on BMD in the spine and hip and reduces the risk of osteoporotic fractures. The Vertebral Efficacy with Risedronate Therapy (VERT) trials [Harris 1999; Reginster 2000], documented approximately 40% reductions in the risk of vertebral fractures. These reductions were sustained for at least five years. [Harris 1999; Reginster 2000] Reductions in hip fractures were shown in a large study, the Hip Intervention Program (HIP), that included over 9000 women. In women aged 70 to 79 years with severe osteoporosis and other risk factors for fracture, a 40% reduction in the incidence of hip fractures was seen by the third year in patients who received risedronate. However, in patients over 80 without proven osteoporosis but with other risk factors, risedronate-treatment groups had no significant reduction in hip fractures. [McClung 2001] These results are surprising and several explanations are possible, including the characteristics of the particular patient population. Risedronate has also recently been approved for once-weekly dosing.

A recent addition to the armamentarium of non-estrogen therapies for osteoporosis is a derivative of human parathyroid hormone (PTH). The recombinant form of PTH, consisting of amino acids 1-34, was approved in 2002 as Forteo® (teriparatide; Lilly), a subcutaneously administered injection. Once-daily administration of PTH stimulates osteoblastic activity preferentially through specific receptors. Increases in bone mass and strength, as well as increases in markers of bone turnover, are the result. [Forteo PI] ◀ **ANABOLIC THERAPY**

This agent was evaluated in 1637 postmenopausal women with prior vertebral fractures in a randomized placebo-controlled trial. Patients who received 20 µg/d and 40 µg/d doses of PTH had increased BMD overall and in the lumbar spine and femoral neck specifically, relative to placebo. New vertebral fractures occurred in 14% of women in the placebo group and in 5% and 4%, respectively, of the women in the 20-µg group and the 40-µg group. The risk of nonvertebral fractures was reduced by more than 50% in the two treatment groups. [Neer 2001]

A meta-analysis of controlled trials provides an estimate of the comparative efficacy of these therapies (with the exception of PTH) for prevention and treatment of osteoporosis. [Cranney 2002] Although direct comparisons between trials are unreliable, strong data are apparent for alendronate and risedronate as first-line therapy. [Cranney 2002] In addition, a recent comparison across trials of antiresorptive therapies suggested that alendronate was more effective than risedronate, calcitonin, raloxifene, and hormone therapy for reducing the risk of vertebral and nonvertebral fractures. Significant differences were found between alendronate and calcitonin for vertebral fractures and between alendronate and risedronate, calcitonin, estrogen, and raloxifene for nonvertebral fractures. [Wehren 2004] ◀ **SUMMARY**



## CONCLUSIONS

Recent events have increased the importance of non-estrogen therapies for patients with osteoporosis. Bisphosphonates have emerged as significant first-line therapy for prevention and treatment of osteoporosis in postmenopausal women. In particular, long-term clinical experience and new long-term data with alendronate supports use of this agent for many patients with or at risk for osteoporosis.

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**CME Post-Test Questions** Seven correct answers are required for credit

- Calcitonin works through binding to hydroxyapatite in bone.
 

<input type="checkbox"/> A. True	<input type="checkbox"/> B. False
----------------------------------	-----------------------------------
- Recent clinical trials have shown continuing increases in BMD associated with alendronate therapy compared with placebo over \_\_\_\_\_.
 

<input type="checkbox"/> A. 5 years	<input type="checkbox"/> C. 8 years
<input type="checkbox"/> B. 10 years	<input type="checkbox"/> D. 2 years
- A recent study indicated that only \_\_\_\_\_ of patients with fractures had previously received a diagnosis of osteoporosis.
 

<input type="checkbox"/> A. 12%	<input type="checkbox"/> C. 44%
<input type="checkbox"/> B. 79%	<input type="checkbox"/> D. 38%
- Changes to guidelines for initiating osteoporosis therapy were recently issued from:
 

<input type="checkbox"/> A. The American College of Obstetricians and Gynecologists	<input type="checkbox"/> C. Smoking
<input type="checkbox"/> B. The American Medical Association	<input type="checkbox"/> D. All of the above
<input type="checkbox"/> C. The National Osteoporosis Foundation	
<input type="checkbox"/> D. Congress	
- Bone turnover markers reflect the activity of \_\_\_\_\_.
 

<input type="checkbox"/> A. Osteoblasts and osteoclasts	<input type="checkbox"/> C. Fractures
<input type="checkbox"/> B. Calcium	<input type="checkbox"/> D. Age
- Endogenous calcitonin is secreted by \_\_\_\_\_.
 

<input type="checkbox"/> A. The liver	<input type="checkbox"/> C. Osteoclasts
<input type="checkbox"/> B. The thyroid gland	<input type="checkbox"/> D. The ovaries
- Recombinant parathyroid hormone is administered by \_\_\_\_\_.
 

<input type="checkbox"/> A. Subcutaneous injection	<input type="checkbox"/> C. Nasal spray
<input type="checkbox"/> B. Intramuscular injection	<input type="checkbox"/> D. Oral tablets
- Raloxifene interactions with the estrogen receptor produce some, but not all, the effects of estrogen.
 

<input type="checkbox"/> A. True	<input type="checkbox"/> B. False
----------------------------------	-----------------------------------
- Which patient characteristics are important risk factors for osteoporotic fractures?
 

<input type="checkbox"/> A. Thin build	<input type="checkbox"/> C. Smoking
<input type="checkbox"/> B. History of prior fractures	<input type="checkbox"/> D. All of the above
- Meta-analyses of alendronate efficacy suggest approximately \_\_\_\_\_ reduction in risk of hip fractures during treatment of postmenopausal women.
 

<input type="checkbox"/> A. 23%	<input type="checkbox"/> C. 50%
<input type="checkbox"/> B. 33%	<input type="checkbox"/> D. 5%

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## POST-TEST ANSWERS

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# OSTEOPOROSIS: THE ERA OF THE BISPHOSPHONATES PART 3

Activity Number: END IN 09 101 04

Expiration date: 08-31-06

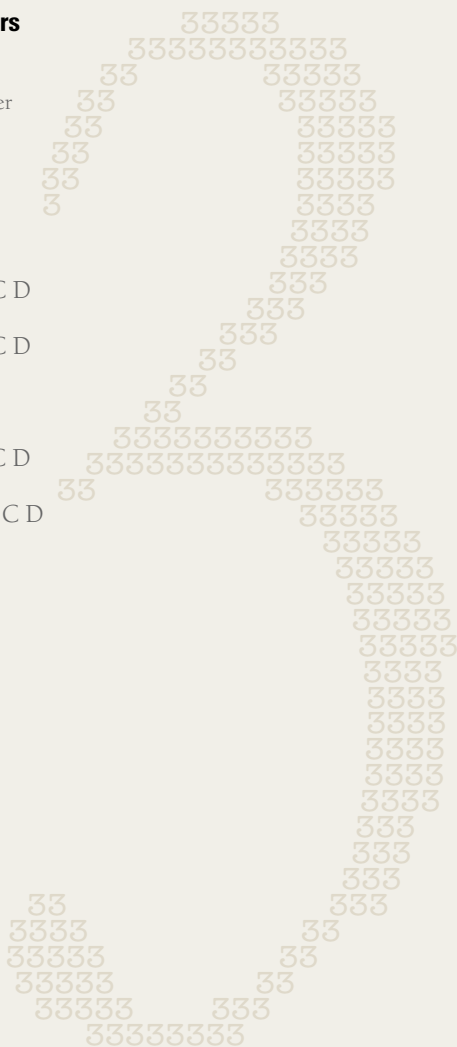
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### CME Post-Test Answers

(Circle the appropriate letter for each question.)

- |            |             |
|------------|-------------|
| 1. A B     | 6. A B C D  |
| 2. A B C D | 7. A B C D  |
| 3. A B C D | 8. A B      |
| 4. A B C D | 9. A B C D  |
| 5. A B C D | 10. A B C D |



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# ACTIVITY EVALUATION

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## Activity Evaluation

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1. As a result of the information contained in this activity, will you make any changes in your practice? Yes \_\_\_\_\_ No \_\_\_\_\_

If yes, what changes? \_\_\_\_\_  
\_\_\_\_\_

2. In your opinion, how could this activity be improved? (e.g., change format, more details, fewer details, discuss other topics, change length) \_\_\_\_\_  
\_\_\_\_\_

3. Please rate the educational value/clinical relevance of this activity.

\_\_\_\_\_ Excellent/outstanding \_\_\_\_\_ Very good \_\_\_\_\_ Good/above average  
\_\_\_\_\_ Fair/acceptable \_\_\_\_\_ Poor/unacceptable

4. Please rate the extent to which the learning objectives were met.

\_\_\_\_\_ Excellent/outstanding \_\_\_\_\_ Very good \_\_\_\_\_ Good/above average  
\_\_\_\_\_ Fair/acceptable \_\_\_\_\_ Poor/unacceptable

5. Was the material presented objectively and did it avoid commercial bias?

Yes \_\_\_\_\_ No \_\_\_\_\_ Comments: \_\_\_\_\_  
\_\_\_\_\_

6. Suggestions for future topics: \_\_\_\_\_  
\_\_\_\_\_

7. Other comments: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

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## Personal Information

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Name/degree (please print) \_\_\_\_\_

Address \_\_\_\_\_

City \_\_\_\_\_ State \_\_\_\_\_ Zip \_\_\_\_\_

Telephone \_\_\_\_\_

Last four digits of Social Security Number \_\_\_\_\_

Please submit this form, along with your check for \$15.00 payable to CPDE and mail in the enclosed envelope to:

CPDE Registrar  
P. O. Box 980048  
Richmond, VA 23298-0048

Or you may pay by credit card and fax your form to us at 804-828-7438

MasterCard \_\_\_\_\_ VISA \_\_\_\_\_ Discover \_\_\_\_\_ AMEX \_\_\_\_\_

Name as it appears on card \_\_\_\_\_

Credit card number \_\_\_\_\_

Signature \_\_\_\_\_ Expiration Date \_\_\_\_\_

I have listened to the CD, read the monograph, and completed the post-test and activity evaluation.

Signature \_\_\_\_\_ Date \_\_\_\_\_  
\_\_\_\_\_