



CLINICAL UPDATE

The Clinical Efficacy and Safety of Tretinoin for the Treatment of Aging Skin

Improving the appearance of aging skin is an important objective for dermatologists and their patients. There are a variety of surgical techniques and skin care regimens that dermatologists can use to achieve the cosmetic goals of the patient. One of the most

commonly prescribed topical treatments for aging skin is tretinoin, or all-trans retinoic acid. This continuing education supplement will describe the characteristics of tretinoin and detail the clinical research that demonstrates the effectiveness of tretinoin for aging skin.

ACCREDITATION STATEMENT

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Term of Approval: June 2009 - June 30, 2010

Estimated time to complete this educational activity: .75 hour

TARGET AUDIENCE

This activity has been developed for plastic surgeons, dermatologists, and other health care professionals involved in the use of aesthetic/cosmetic treatments.

LEARNING OBJECTIVES

At the end of this educational activity, participants should be able to:

- Classify the major causes of aging
- Discuss the cellular impact that photodamage has on the skin
- Detail the important clinical attributes of tretinoin for the treatment of photoaging.

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Skin Damage Due to Chronological Aging and Photodamage

To understand how to treat aging skin, it is important to understand the intrinsic and extrinsic factors that contribute to the aging process. Intrinsic aging refers to changes in the cellular structure of skin caused by genetic and other endogenous influences.¹ Extrinsic factors that affect aging include photodamage and other environmental stressors such as cigarette smoke and smog.²⁻⁴ Excessive exposure to ultraviolet (UV) radiation through sunlight is the biggest culprit of skin damage, leading to the wrinkles, altered pigmentation, and loss of skin tone that characterize aging.^{2,5}

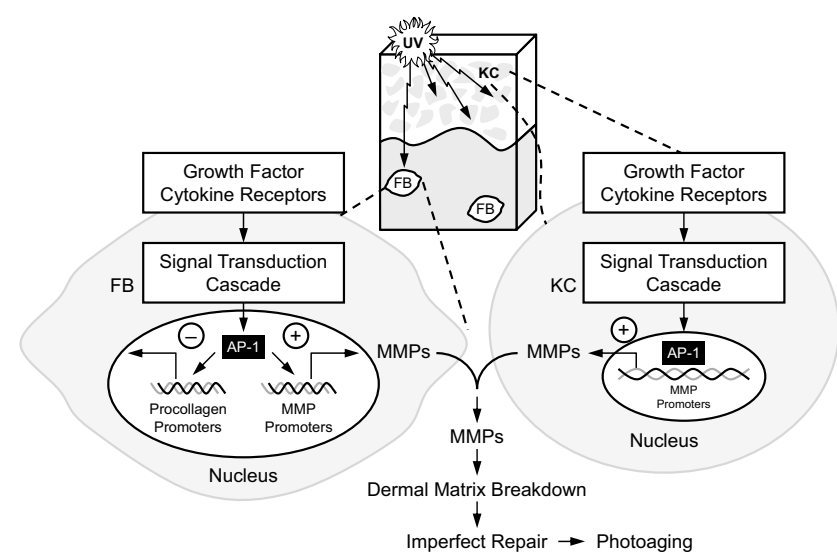
The cellular and molecular mechanisms that cause both chronological aging and photoaging have been studied extensively. It appears that both types of aging

share the same molecular pathways, which may lead to new therapies for the treatment of aging skin. UV light (UV radiation [UVR]) affects skin through a series of cellular and molecular events. UVR activates cell surface growth factors and cytokine receptor signaling pathways that alter expression of genes such as metalloproteinases, the enzymes that break down collagen. UVR also activates transcription factors such as activator protein-1 (AP-1) that impair collagen synthesis and stimulate transcription of proinflammatory mediators, including several interleukins and tumor necrosis factor- α . Through these molecular events, UV light reduces collagen synthesis and enhances collagen breakdown, affecting both the appearance and the structural integrity of the skin (Figure 1).³

The Role of Retinoids in Treating Photodamage

Although many cosmetic and cosmeceutical products claim to improve the appearance of skin that is photodamaged, most of these products either cover up the damage or soothe the irritated skin without actually improving the skin on a cellular level.^{3,6} Retinoids, on the other hand, have been proven through a large number of clinical studies to improve the appearance of aging skin at the cellular level following topical application.³ Retinoids, specifically

Figure 1. UV Radiation Causes Photodamage on a Molecular Level



UV=ultraviolet; FB=fibroblast; KC=keratinocyte; AP-1=activator protein-1; MMP=metalloproteinase.
Source: Fisher et al³

Reprinted with permission from Fisher GJ, Kang S, Varani J, et al. Mechanisms of photoaging and chronological skin aging. *Arch Dermatol*. 2002;138:1462-1470.

topical vitamin A acid (retinoic acid or tretinoin), were first used to treat acne vulgaris 40 years ago,⁷ and since that time, the use of retinoids has branched out to include treatments for hyperpigmentation, rosacea, and photodamage.⁸ Most marketed brands of tretinoin are approved only for the treatment of acne vulgaris and only one is approved for the treatment of photodamaged skin.

On a molecular level, retinoids are important molecules that have revolutionized dermatologic therapy because of their biologic diversity.⁸ The cellular effects of retinoids include anticancer properties when used topically on precancerous or cancerous neoplasms, anti-inflammatory properties as seen with treatment of acne and psoriasis, and epithelial proliferation and differentiation as noted with treatment of photodamage.⁸

The mechanism of action of tretinoin leads to clues about its effectiveness in the treatment of photodamage. The application of tretinoin to the skin initiates a series of events that can both prevent and repair photodamage.³ When applied topically to the skin, tretinoin enters skin cells and binds to nuclear hormone receptors, including retinoid X receptors and retinoic acid receptors. It is this activated retinoid-receptor complex that allows retinoids to inhibit or activate transcription of certain genes.⁹

Studies with human skin demonstrate that pretreatment with topical tretinoin reduces UVR-induced expression of the transcription factor AP-1.³ This action downregulates production of enzymes that degrade collagen and, thus, preserves dermal collagen. In addition, when collagen loss has already occurred, the application of topical tretinoin induces procollagen gene expression.¹⁰ These combined effects explain how tretinoin boosts dermal collagen.

Efficacy of Tretinoin for Treatment of Photodamaged Skin

The first double-blind, vehicle-controlled study of tretinoin for photoaged skin was reported by Weiss et al¹¹ in 1988. In this 16-week trial, 30 patients used tretinoin 0.1% cream on one forearm and vehicle cream on the other once daily for 4 months. Half of the patients also applied tretinoin to their faces, and the other half applied vehicle cream to their faces. All 30 patients showed a statistically significant improvement in photoaging on the forearm treated with tretinoin ($P < 0.0001$), and 14 of 15 patients who received tretinoin on their faces reported improvement. However, although patients treated with tretinoin demonstrated a statistically significant improvement in coarse wrinkles ($P < 0.01$), roughness ($P < 0.02$), and fine wrinkling ($P < 0.0001$) on their

forearms and faces, irritation related to tretinoin application was reported by 92% of patients.

In addition to the improved appearance of the skin that tretinoin provides for photodamaged skin, there are also histologic effects of tretinoin demonstrating that tretinoin works below the skin as well as on the surface of the skin. Bhawan and colleagues¹² reported histologic changes in the skin following 24 weeks of tretinoin treatment. Tretinoin increased epidermal thickness, increased granular layer thickness, decreased epidermal melanin content, and promoted stratum corneum compaction. All of these changes improve the appearance of the skin.

One of the early marketed formulations of tretinoin was tretinoin 0.05% emollient cream. Key clinical studies for this emollient cream demonstrated substantial improvement in fine wrinkles, mottled hyperpigmentation, and roughness of facial skin when used in combination with a sun avoidance and sun protection program.¹³ Two key clinical trials were conducted in a total of 218 patients treated with tretinoin 0.05% or 0.01% emollient cream and 154 patients treated with vehicle emollient cream on the face for 24 weeks.^{14,15} Both of these studies compared tretinoin 0.05% emollient cream with tretinoin 0.01% emollient cream and demonstrated increased tolerability of the lower-concentration formulation compared to that of the higher-concentration formulation. In addition, patient response to tretinoin was graded for eight clinical signs of photodamage, including fine wrinkling, coarse wrinkling, mottled hyperpigmentation, lentigines, roughness, laxity, telangiectasia, and yellowing. A global score was calculated based on these eight clinical signs. Investigators reported better global improvement with tretinoin cream compared to that

with vehicle.^{14,15} In addition, a 2-year study with tretinoin 0.05% emollient cream demonstrated long-term efficacy and safety of this treatment.¹⁶

One ongoing concern with tretinoin cream is the skin irritation that patients report during use, such as burning, stinging, erythema, peeling, dry skin, and pruritus.¹³⁻¹⁶ To determine whether irritation is necessary for efficacy, one study examined 2 concentrations of tretinoin cream (0.1% and 0.025%).¹⁷ In this study, patients applied tretinoin cream once daily for 48 weeks. Investigators found that although clinical improvement was equal in both groups, irritation was reduced for patients using the lower-concentration cream. This study led to development of a lower-dose tretinoin 0.02% cream.

Efficacy of Tretinoin 0.02% Cream for Photodamage

Tretinoin 0.02% cream is a lower-concentration cream formulation that has been shown to reduce fine facial wrinkles when used in combination with a comprehensive sun avoidance and skin care regimen. Tretinoin 0.02% cream has been studied in four well-controlled, multicenter clinical trials and one single-center, randomized, controlled trial. A total of 324 patients were treated for 24 weeks with tretinoin 0.02% cream and 332 patients were treated for 24 weeks with vehicle cream.¹³ Two of the five clinical trials demonstrated efficacy in reducing the appearance of fine facial wrinkling after 6 months of treatment.¹³

Tretinoin 0.02% cream is also effective for up to 1 year of treatment. Patients who participated in a 24-week study were allowed to continue in a long-term extension study following a 12-week off-therapy phase.¹⁸ Results from this multicenter, open-label, 52-week exten-

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Table 1. Improvement Compared to Baseline for Patients After 52 Weeks of Treatment With Tretinoin 0.02% Cream

Rating Compared With Baseline	Tretinoin 0.02% Cream (n=108)
Improved, n (%)	92 (85)
Much improved	20 (19)
Improved	39 (36)
Slightly improved	33 (31)
No change, n (%)	16 (15)
Worse, n (%)	0 (0)
Mean score*	3.6

*Score rating=1 (worse), 2 (no change), 3 (slightly improved), 4 (improved), 5 (much improved).
Source: Nyirady et al¹⁸

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sion trial demonstrated that in the investigators' global evaluation of efficacy, 85% of patients treated with tretinoin 0.02% cream were considered "improved" compared with baseline (Table 1).¹⁸ No patients had worsening of their photodamaged skin. In addition, this study demonstrated a reduction in fine wrinkling, which improved during the 52 weeks of the study (Figure 2).¹⁸ Overall, both patients and physicians saw improvements in severity of photodamage, fine wrinkling, and overall appearance with the use of tretinoin 0.02% cream.

The safety data from this long-term clinical trial demonstrated that tretinoin 0.02% cream was generally well tolerated and had a favorable safety profile. Signs and symptoms of irritation (erythema, peeling, and burning/stinging) were highest at 4 weeks

and then declined to baseline by 8 weeks. Overall, 43% of patients reported skin irritation during the 52-week trial, but the irritation was generally mild or moderate. Only 6% of patients discontinued the long-term study because of adverse events.¹⁸

In a separate study, Nyirady and colleagues¹⁹ compared the irritation factor of several commonly used retinoid formulations, including tretinoin 0.02% cream. Sixty healthy adults were randomized to six groups: tretinoin 0.02% cream, tretinoin 0.05% emollient cream, tretinoin 0.05% cream, tretinoin 0.1% cream, tazarotene 0.1% cream, or tazarotene 0.1% gel. Patients were treated 3 times weekly for 3 weeks and evaluated using an irritation score. This study demonstrated that tretinoin 0.02% cream was the least irritating of the six preparations studied.

Efficacy of Tretinoin in Combination With Other Cosmetic Procedures

Tretinoin 0.02% cream is approved for the mitigation of facial wrinkles in patients who use a comprehensive skin care and sunlight avoidance program. However, tretinoin emollient cream has also been used off-label in combination with a variety of cosmetic procedures to enhance the cosmetic effects of these procedures and to potentially speed wound healing. Cosmetic procedures such as dermabrasion, chemical peels, and laser skin resurfacing are used to rejuvenate the skin by inducing a wound on the skin surface and allowing the skin to heal.²⁰ With a proper skin care regimen, the healing time can be reduced and improvements in the final cosmetic result are possible. Because tretinoin has been proven to increase epidermal thickness and increase granular layer thickness,¹² tretinoin use pre- or post-cosmetic procedure may improve cosmetic outcomes.²⁰ Tretinoin treatment before a wounding procedure has been studied using animal models where pretreatment with tretinoin accelerated healing of partial-thickness wounds.²⁰ These models may be applicable to human use. In addition, the Guidelines of Care on chemical peeling published in 1995 by the American Academy of Dermatology recommended preoperative and postoperative treatment with tretinoin.²¹

Dermabrasion is a common procedure used to improve the appearance of photodamaged skin, wrinkles, and facial scarring. The use of tretinoin before and after dermabrasion has been shown to be beneficial.²² This study enrolled 123 patients, and 88 patients received 2 weeks of pretreatment with tretinoin 0.05% cream. The patients who received tretinoin had substantially faster healing (7 days), and no milia or postinflammatory hyperpigmentation occurred. Patients who did not receive tretinoin healed in an average of 11 days, and 28% of those patients had milia and/or hyperpigmentation following dermabrasion.

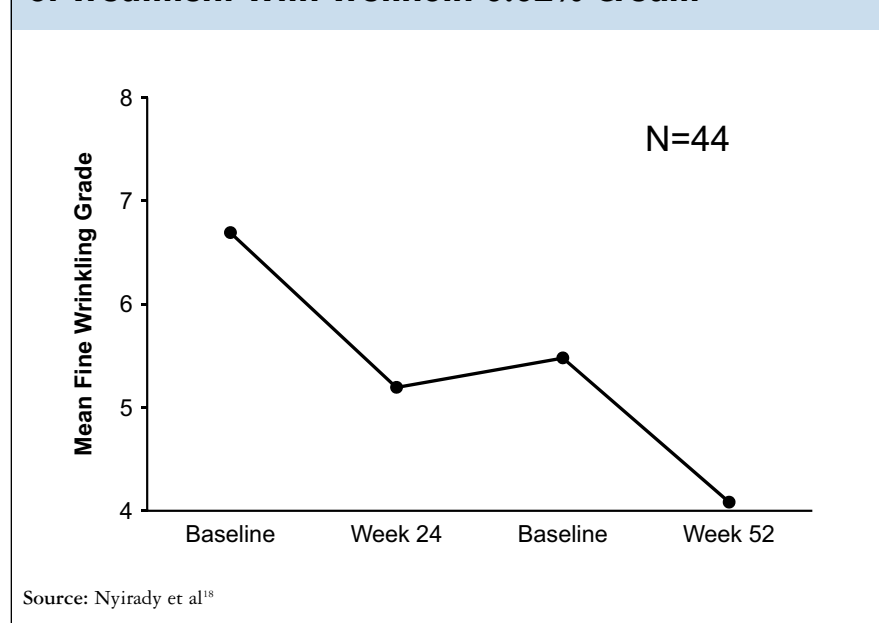
The use of tretinoin before trichloroacetic acid (TCA) peel has also been examined, and two studies show conflicting results.^{23,24} Hevia and colleagues²³ conducted a double-blind, placebo-controlled study in 16 men with actinically damaged skin. These

patients were treated daily with tretinoin 0.1% or placebo on the left and right sides of the face, forearms, and hands, respectively, for 14 days prior to a TCA peel. The results of this study showed that the face demonstrated the fastest healing time and that pretreatment with tretinoin led to improved healing time. However, there was no clinical difference between the final results achieved with tretinoin and those achieved with TCA peel only. The other study, conducted by Humphreys and colleagues,²⁴ examined 16 men with actinic damage, including actinic keratoses. Eight patients were pretreated with tretinoin for 6 weeks prior to TCA peel. Some improvements were seen for all patients, and more rapid and even frosting was observed in the group of patients treated with tretinoin. The study concluded, however, that the use of tretinoin did not significantly enhance the efficacy of the peel.

Tretinoin use before and after laser skin resurfacing is common. A survey in 1998 demonstrated that 80% of dermatologists and plastic surgeons recommended pretreatment with tretinoin to improve wound healing and cosmetic outcomes following laser skin resurfacing.²⁵ A number of studies on the use of tretinoin for laser skin resurfacing are summarized in Table 2.^{20,26-30} These studies demonstrated a variety of beneficial effects with tretinoin treatment, including minimizing hyperpigmentation,^{26,28,30} improved wound healing,²⁷ and improved scarring.²⁹

Tretinoin has also been shown to improve healing times after electroepilation.³¹ In this study, five patients were pretreated on one groin or axilla with tretinoin 0.05% emollient cream for 2 weeks prior to electroepilation. Electroepilation creates small, superficial wounds during the destruction of hair follicles. Skin on the pretreated side showed significantly decreased healing time compared to the non-pretreated side ($P=0.03$).³¹

Pretreatment with tretinoin in combination with cosmetic procedures may improve healing times by enhanced re-epithelialization and reduce postoperative complications such as milia and hyperpigmentation. More studies are necessary to fully explore the utility of tretinoin in these clinical situations.

Figure 2. Change in Fine Wrinkling After 52 Weeks of Treatment With Tretinoin 0.02% Cream

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Table 2. Summary of Studies Examining Tretinoin Therapy Before and After Laser Resurfacing

Author(s)	Skin Condition	Subjects, N	Pretreatment	Posttreatment	Results
Lowe et al	Photodamage*	30	Tretinoin 0.025% or 0.05% cream nightly for 4 weeks	Tretinoin 0.025% or 0.05% cream nightly, started 4 weeks after laser resurfacing	Pretreatment optimizes response to laser surgery, and posttreatment minimizes hyperpigmentation
Apfelberg	Facial rhytides, acne scarring, and photoaging*	11	Tretinoin 0.05% or 0.1% cream for 3-6 weeks		Optimal wound healing in 9 days
Ho et al	Facial rhytides and scars [†]	30	Tretinoin 0.05% cream for 2-4 weeks	Tretinoin 0.05% cream 4-6 weeks after laser resurfacing	Hyperpigmentation reduced
Kye	Pitted facial scars [†]	30	Tretinoin 0.05% cream nightly for 2-4 weeks	Tretinoin 0.05% cream 2-4 weeks after laser resurfacing	40% to 55% improvement in scars
Weinstein	Wrinkles, scars, and rhinophyma*	2123		Retinoic acid 0.05% to 0.1% for 10-14 days after laser resurfacing	Pretreatment ineffective; posttreatment in darker skin types (Fitzpatrick IV-VI) reduces hyperpigmentation and prevents milia and acne

*Carbon dioxide laser skin resurfacing.

[†]Er:YAG laser skin resurfacing.Sources: Nyirady et al,²⁰ Lowe et al,²⁶ Apfelberg,²⁷ Ho et al,²⁸ Kye,²⁹ Weinstein³⁰Reprinted with permission from *Cosmetic Dermatology*. 2003;16(5):39-44, 47. ©2003, Quadrant HealthCom Inc.

Conclusions

Cosmetic improvement of aging skin is an important clinical goal for dermatologists and their patients. Although the best prevention for facial wrinkles and photodamage is sun avoidance and proper skin care, use of tretinoin may improve the skin once the sun damage has been done. A number of clinical studies have demonstrated that the use of tretinoin 0.02% cream can improve photodamage and facial wrinkles and may improve healing time when used in combination with different physical modalities such as laser resurfacing and microdermabrasion. ■

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EDUCATIONAL NEEDS

Improving the appearance of aging skin is an important objective for dermatologists, and their patients. According to the American Society for Aesthetic Plastic Surgery, nonsurgical procedures for improving the look of the skin are now preferable to surgical procedures as evidenced by the fact that there were 8.4 million nonsurgical cosmetic procedures performed in 2008 compared to only 1.7 million surgical cosmetic procedures.¹ In general, consumers tend to favor noninvasive treatments because they are less costly, have little to no downtime, and have fewer side effects. Additionally, consumers favor over-the-counter cosmeceuticals and prescription antiaging medications for facial rejuvenation. Dermatologists prescribe these products to enhance results obtained from in-office procedures and as part of a comprehensive antiaging regimen. Dermatologists need to stay educated about the clinical research regarding antiaging medications and procedures.

Tretinoin is a commonly prescribed cream for treatment of photoaged skin. In clinical studies, tretinoin cream has been shown to improve fine wrinkles, mottled hyperpigmentation, and roughness of facial skin as a result of photodamage.² Tretinoin is also safe and effective for long-term (up to 2 years) treatment.³ In order for tretinoin to be most effective, it should be used in combination with a sun avoidance and sun protection program.² In addition, there is some research that suggests that tretinoin, in combination with other cosmetic procedures, increases healing time and improves the appearance of the skin.⁴ More clinical research is needed to determine the appropriate role for tretinoin in cosmetic procedures. However, in the meantime, there remains a need for continued education of dermatologists about the available treatments for photodamage as patients are becoming more informed about different options to improve the appearance of their skin.

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CME QUESTIONS

Instructions: For each question or incomplete statement, choose the answer or completion that is correct. Circle the most appropriate.

- Which of the following is the biggest cause of skin aging?
A. Smog
B. Cigarette smoke
C. Natural aging process
D. Sunlight
- What was the first clinical use for retinoids?
A. Photoaging
B. Acne
C. Rosacea
D. Hyperpigmentation
- Which concentration of tretinoin was used in the first double-blind, vehicle-controlled clinical study?
A. 0.02%
B. 0.05%
C. 0.1%
D. 0.5%
- Which of the following histologic changes occur(s) in the skin after tretinoin treatment for 24 weeks?
A. Increased epidermal thickness
B. Increased granular layer thickness
C. Decreased epidermal melanin content
D. All of the above
- Which of the following adverse effects are reported with the use of tretinoin cream?
A. Burning
B. Stinging
C. Erythema
D. All of the above
- Which of the following showed the least irritation in the study by Nyirady and colleagues in 2003?
A. Tretinoin 0.02% cream
B. Tretinoin 0.05% emollient cream
C. Tazarotene 0.1% cream
D. Tazarotene 0.1% gel

EVALUATION FORM

We would appreciate your answering the following questions in order to help us plan for other activities of this type.

PLEASE PRINT
(All information is confidential.)

Name: _____ Specialty: _____

Degree: MD DO PharmD RPh NP RN BS PA Other _____

Affiliation: _____

Address: _____

City: _____ State: _____ Zip: _____

Telephone: _____ Fax: _____

E-mail: _____

Signature: _____

CME CREDIT VERIFICATION

I verify that I have spent _____ hour(s)/_____ minutes of actual time working on this CME activity. No more than .75 CME credit(s) will be issued for this activity.

PRETEST ASSESSMENT: Please rate your current knowledge of photoaging on a scale of 1 to 5, with 1 being the lowest and 5 the highest. 1 2 3 4 5

POST-TEST ASSESSMENT: Please rate your current knowledge of photoaging on a scale of 1 to 5, with 1 being the lowest and 5 the highest. 1 2 3 4 5

COURSE EVALUATION: Please evaluate the effectiveness of this activity by circling your choice on a scale of 1 to 5, with 1 being the lowest and 5 the highest.

- Classify the major causes of aging 1 2 3 4 5
- Discuss the cellular impact that photodamage has on the skin 1 2 3 4 5

3. Detail the important clinical attributes of tretinoin for the treatment of photoaging 1 2 3 4 5

4. How do you rate the overall quality of the activity? 1 2 3 4 5

5. How do you rate the educational content of the activity? 1 2 3 4 5

6. After participation in this activity, have you decided to change one or more aspects in the treatment of your patients? Yes No
If yes, what change(s) will you make? _____

If no, why not? _____

7. Was the presented information fair, objective, balanced, and free of bias in the discussion of any commercial product or service? Yes No
If no, please comment: _____

8. Suggested topics for future activities: _____

9. Suggested authors for future activities: _____

10. Would you be willing to participate in postactivity follow-up surveys? Yes No

11. Would you be willing to participate in a phone, e-mail, or in-person discussion exploring ways to improve our CME activities? Yes No

The EOCME thanks you for your participation in this CME activity. All information provided improves the scope and purpose of our programs and your patients' care.