Highlights from a symposium held during the 25th Hawaii Dermatology Seminar
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Maui, Hawaii

Update of TOPICAL RETINOID Therapy in Acne

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CME Overview

CME Overview and Intended Audience
Update of Topical Retinoid Therapy in Acne is a continuing medical education activity for dermatologists. The goal of this publication is to update dermatologists on the use of topical retinoids in the treatment of acne vulgaris and to highlight special considerations relating to such therapy in darker-skinned patients. This publication reviews the clinical efficacy and tolerability of topical retinoid therapy using recently available data from well-controlled clinical trials.

Readers may use the newly acquired information in this activity to enhance their own professional development and improve patient outcomes. The information presented in this activity is not meant to serve as a guideline for patient management; primary references and full prescribing information should be consulted.

Educational Objectives
Upon completion of this supplement, participants should be able to:

• Compare the efficacy of several topical retinoid formulations used in the treatment of acne vulgaris
• Explain how best to optimize the tolerability of topical retinoid therapy
• Describe how best to approach the treatment of acne in darker-skinned patients

Accreditation
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Center for Advanced Medical Education and ApotheCom Associates, LLC. The Center for Advanced Medical Education is accredited by the ACCME to provide continuing medical education for physicians.

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Estimated time to complete this educational activity: 1 hour

Authors’ Disclosure Statements

Alan R Shalita, MD
Dr Shalita has disclosed that he receives grants/research support and honoraria from Allergan, Inc., Dermik Laboratories, Inc., Estee Lauder, Galderma Laboratories, L.P., Johnson and Johnson, Ortho Dermatological, Medicis, The Dermatology Company, and Stiefel Laboratories, Inc. He also serves as a consultant to Dermik Laboratories, Inc., Galderma Laboratories, L.P., Johnson and Johnson, Medicis, The Dermatology Company, and Stiefel Laboratories, Inc. Dr Shalita is a stockholder of Johnson and Johnson and Medicis, The Dermatology Company.

The unlabeled/investigational or unapproved use of tretinoin swabs and tazarotene cream will be presented in Dr Shalita’s article.

James J Leyden, MD
Dr Leyden has disclosed that he is a consultant to and receives grants/research support and honoraria from Allergan, Inc., Galderma Laboratories, L.P., Ortho Dermatological, and Roche Pharmaceuticals.

The unlabeled/investigational or unapproved use of tazarotene cream will be presented in Dr Leyden’s article.

Pearl E Grimes, MD
Dr Grimes has disclosed that she receives grants/research support from Allergan, Inc., Medicis, The Dermatology Company, and PharmaKinetics, and is a consultant to Procter and Gamble Pharmaceuticals, Inc.

The unlabeled/investigational use of the 0.05% formulation of tazarotene gel in the treatment of acne will be presented in Dr Grimes’s article.

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Topical retinoids play a pivotal role in the treatment and prevention of acne lesions. They promote the normalization of follicular epithelial desquamation and reduce cellular cohesion—which not only promotes the drainage of existing comedones but also helps to prevent the development of microcomedones (the precursor of all acne lesions) and thus mature noninflammatory and inflammatory acne lesions. The comedolytic action of topical retinoids enhances the penetration of other agents, and maximum efficacy is usually achieved through the use of a topical antibacterial agent in conjunction with a topical retinoid. Retinoids also have some indirect antibacterial activity through their effects on the follicular microclimate, which makes conditions in the follicle less hospitable to *P. acnes*.

The original studies with topical retinoids in the 1960s and early 1970s used tretinoin 0.05% swabs and demonstrated substantial efficacy against both noninflammatory and inflammatory lesions. Even though it was clear from the outset that topical retinoids are effective against inflammatory lesions as well as noninflammatory lesions (and subsequent research with the newer topical retinoids has confirmed this), for some reason this has often been overlooked and many dermatologists still have a perception that topical retinoids are effective only against noninflammatory lesions. In reality, topical retinoids are also very useful in the clinic against inflammatory lesions, though maybe not as the sole agent.

Although the original tretinoin studies demonstrated efficacy, the formulations also resulted in significant irritation, erythema, and peeling. Over the years, newer and less irritating tretinoin formulations have been introduced, including creams, gels, and a microsponge gel, which have improved tolerability. Research has also resulted in the introduction of two newer retinoids, adapalene and tazarotene.

Although results from one trial1,2 apparently demonstrated adapalene 0.1% gel to be more
effective than tretinoin 0.025% gel in reducing the total lesion count, subsequent clinical experience has not tended to support this notion. Furthermore, despite the general perception that tretinoin is more irritating than adapalene, particularly during the first few weeks of treatment, the results of this trial showed that an almost identical percentage of patients in both groups experienced dryness of their skin after 2 weeks of treatment. Both these rather surprising findings could be explained by a problem with compliance among the tretinoin-treated patients—it is possible that the greater irritation potential of tretinoin led to reduced compliance, which not only artificially lowered its clinical effectiveness but also appeared to improve its tolerability profile in the initial weeks of treatment. Indeed, a second multicenter trial comparing adapalene 0.1% gel with tretinoin 0.025% gel showed that the efficacy of the two drugs was comparable. Overall, tretinoin and adapalene are both effective topical retinoids in the treatment of acne, and the tolerability of each drug may vary from patient to patient.

Tazarotene 0.1% gel has since been shown in multicenter double-blind randomized studies to offer significantly greater reductions in noninflammatory lesions than tretinoin 0.025% gel, tretinoin 0.1% microsponge, and adapalene 0.1% gel, and significantly greater reductions in inflammatory lesions than adapalene 0.1% gel (Figure 1).

Two of the most recently available retinoid formulations are adapalene 0.1% cream (approved for acne vulgaris) and tazarotene 0.1% cream (at present approved for plaque psoriasis only but file pending with FDA for acne). In large-scale, multicenter, double-blind, randomized, parallel-group trials, both these cream formulations achieved significantly greater reductions in total acne lesions than vehicle after 12 weeks of once-daily applications (p < 0.01 for adapalene cream versus vehicle; p < 0.001 for tazarotene cream versus vehicle). And, in terms of inflammatory lesions specifically, tazarotene resulted in a significantly greater reduction in lesion count after 12 weeks of treatment (p < 0.05). Adapalene also reduced inflammatory lesions, but detailed data are not available at this time.

In vehicle-controlled studies with both the gel and cream formulations of tazarotene, and with tretinoin 0.025% cream, the time taken for the retinoid to achieve significantly greater reductions in lesion count than vehicle was longer for inflammatory lesions than for noninflammatory lesions (12 weeks versus 2–4 weeks). Thus, in the treatment of inflammatory acne in particular, it is important to start topical retinoid therapy early and to continue it for at least 3 months to ensure an adequate timeframe for clinical improvement. Also, to help hasten the speed of clinical improvement, it will likely be helpful to use another anti-acne medication in conjunction with the topical retinoid. And finally, in order to sustain clinical improvement, it is important to continue with topical retinoid therapy as maintenance therapy.

**Table 1. Key points on topical retinoid therapy for acne.**

- Primary treatment for most forms of acne (inflammatory as well as noninflammatory lesions)
- Use early (for maximum benefit and to reduce the risk of scarring)
- Use for maintenance as well as treatment (to prevent development of new lesions)
REFERENCES


3. Webster GF, Berson D, Stein LF, Fivenson DP, Tanghetti EA, Ling M. Efficacy and tolerability of once-daily tazarotene 0.1% gel versus once-daily tretinoin 0.025% gel in the treatment of facial acne vulgaris: a randomized trial. *Cutis.* 2001; 67 (suppl 6S) (In press).


7. Data on file, Allergan, Inc.


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**Figure 2.** Patient with predominantly inflammatory acne treated with tretinoin 0.025% gel once daily.

**Figure 3.** Patient with predominantly inflammatory acne treated with tazarotene 0.1% gel once daily.
Topical retinoids have a potential for irritation, particularly in “sensitive skin” patients. In addition to observations made during clinical trials, there now are other methodologies for assessing the irritation potential of agents used on the face. Soap and detergent manufacturers have developed protocols for objectively assessing the potential irritancy of products that come into contact with facial skin. These same protocols are now proving of use in comparative evaluations of the potential irritancy of topical retinoids. Although such protocols offer objective means of comparing different products, the methodological requirements necessary to achieve highly controlled conditions of measurement do not necessarily reflect those occurring in everyday clinical practice and may overestimate the true incidence and severity of irritation. Nevertheless, these procedures are useful for studying the relative irritant potential of the many concentrations and formulations of the three topical retinoids currently available.

In one recent split-face study, the tolerability of three topical retinoid formulations (tazarotene 0.1% cream, adapalene 0.1% gel, and tretinoin 0.1% microsponge) were compared in 48 healthy volunteers. Each volunteer was treated with two of the retinoids once daily for up to 28 days, with one retinoid applied to one side of the face and the other applied to the other side of the face. The application procedure was controlled so that all volunteers received the same predetermined amount of medication. On weekdays, the subjects came into the laboratory to have the medication applied by study monitors and on weekend days the subjects applied the medication themselves at home. Unlike the situation in everyday clinical practice, subjects continued to be treated with the same amount of medication each day even if irritation developed and they were not permitted to use a moisturizer. These study conditions were designed to minimize variables in order to provide a clearer view of the irritation potential of the test agents. By minimizing variables (by ensuring the amount of medication applied was the same in all subjects on at least 5 days each week, thus avoiding compliance issues), we can be confident that the study contained only two major variables—the person and the drug. The results of the study showed that all three formulations rated comparably in terms of skin comfort (Figure 1), burning/stinging, erythema, and dryness. (Skin comfort and burning/stinging were rated by the subjects themselves, and erythema and dryness were rated by expert graders.)

In another split-face study, we recruited 60 individuals who had relatively sensitive skin (according to their history or our personal experience with them in other protocols). This type of panel addresses the question of irritation in sensitive patients—an important subset of dermatologic practice.

This study involved subjects applying two of the following, one to each side of their face, once daily for up to 28 days: tazarotene 0.1% gel, adapalene 0.1% gel, tretinoin 0.1% microsponge, and tretinoin 0.025% gel. The results of the study showed that all retinoid formulations were associated with comparable levels of local irritation and that this was greatest during the first week of treatment. The magnitude of these reactions was generally of the type that would likely be controllable through use of a non-comedogenic moisturizer (which patients were not permitted to use in the study). A sub-analysis of only those patients who needed to modify the strictly controlled treatment regimen because of irritation showed that, in this more sensitive subgroup of already sensitive individuals, tazarotene resulted in greater mean levels of irritation than the other retinoids.

Taken together, the results of both these studies...
suggest that the level of irritation that subjects may experience is determined more by patient vulnerability than by the inherent irritant potential of different retinoids. Our observations lead us to conclude that patients with a history of atopy or a tendency toward rosacea are more vulnerable to experiencing irritation with the topical retinoids. A study some years ago of such individuals who had both an atopic background and a tendency toward rosacea showed that, although tretinoin 0.1% microsponge slowed the rate of subjects discontinuing topical retinoid therapy due to irritation compared with tretinoin 0.1% cream, it did not prevent all patients from eventually discontinuing.\(^1\) All of our studies suggest that the sensitivity of an individual’s skin plays a greater role than the retinoid formulation in determining the tolerability of topical retinoid therapy. In our irritation protocols, patients have the same amount of medication applied each day (preventing them from reducing the dose or missing a day if they felt slight irritation, as would be expected to happen in everyday clinical practice) and are not permitted to use moisturizers. Thus, tolerability would be expected to be better among the general population seen in clinical practice than among this population of highly sensitive individuals.

Although there is still much to learn about the causes and nature of sensitive skin, it appears that there are three main physiological factors contributing to the sensitivity of the skin (Table 1). The integrity of the stratum corneum is of primary importance; patients with atopic dermatitis have dry skin and the microfissures in their skin make their epidermis more accessible, and therefore more vulnerable, to potential irritants. The second factor, vascular reactivity, is especially important in individuals with a tendency toward rosacea. And the third factor, difficulty in regulating inflammation, is especially important in patients with atopy. Overall, if the stratum corneum contains microfissures, then topically applied agents can enter the viable epithelium and induce irritation. Individuals with vascular reactivity (e.g. those with rosacea) will likely experience above average erythema, and individuals who have difficulty modifying inflammation (e.g. those with atopy) will likely experience above average irritation.

Generally, it seems that irritation is influenced more by whom we are treating rather than by what we are treating them with. In all patients—but particularly in those with a tendency toward sensitive skin—it is important to minimize the potential for irritation by washing the face gently, using only mild non-soap cleansers, using a non-comedogenic moisturizer, avoiding astringents and other drying agents, applying the topical retinoid sparingly, and initiating therapy gently (with a reduced dose or frequency of dosing). And, because the nasolabial fold and perioral area are more sensitive than other areas of the face, it may be wise to suggest that patients initiate topical retinoid therapy on the forehead first before moving down to the cheeks and finally the central area of the face. It is also helpful to avoid other topical products, such as alpha hydroxy acids, until patients are accommodated to topical retinoid therapy even though these other products may not have a particularly strong potential for irritation themselves.

**Table 2. Treatment approaches to optimize tolerability of topical retinoid therapy.**

- Wash the face gently
- Wash using only a mild non-soap cleanser
- Use a non-comedogenic moisturizer
- Avoid astringents and other drying agents
- Apply the topical retinoid sparingly
- Initiate therapy slowly and gently
- Initiate therapy on the forehead to test skin sensitivity
- Avoid alpha hydroxy acids until accommodated to topical retinoid therapy

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**Table 1. Physiological factors contributing to sensitive skin.**

- Lack of integrity in the stratum corneum
- Vascular reactivity
- Difficulty downregulating inflammation
ne of the most common skin disorders affecting darker-skinned patients is acne.1-4 Although the disease process in acne does not appear to be physiologically and morphologically different in darker skin types, there are general differences in the morphology and physiology of the skin (particularly the epidermis) in African Americans. These differences may influence the absorption of topically applied products and the skin reactivity to certain products, and, as a result, such patients have special issues and needs when being treated for acne.

Some of the main structural and functional differences in skin according to racial origin have been reviewed by Berardesca and Maibach, and a summary is provided in Table 1.5 Darker skin has a relatively higher level of melanin production and the melanocytes tend to overreact to cutaneous injury. Thus, darker-skinned patients are more likely than Caucasian patients to develop postinflammatory dyspigmentation.5,12,13 And African Americans are also more likely to develop postinflammatory dyspigmentation than Asians. Although such dyspigmentation usually takes the form of hyperpigmentation, hypopigmentation may also occur. If dyspigmentation does arise it is usually as a result of inflammatory acne lesions or from treatments that cause an irritant contact dermatitis. More rarely, it may result from allergic contact dermatitis.

A recently published survey of 100 women with darker skin showed that pigmentation problems were one of the most common causes of concern among such individuals.14 As hyperpigmentation can persist for a year or more, it is very important that clinicians ensure their prescribed treatment not only resolves acne lesions but also minimizes the potential for hyperpigmentation. With this in mind, many clinicians may be reluctant to treat their darker-skinned patients with anti-acne medications that are associated with a potential for causing irritation, in case this induces hyperpigmentation or exacerbates existing hyperpigmentation. Products that have been associated with transient irritation include benzoyl peroxide, salicylic acid, glycolic acid and other alpha hydroxy acids, and topical retinoids.14,15 However, such products can be used safely and efficaciously in darker-skinned patients providing that they are titrated upward from a low initial concentration. And, given that topical retinoids are the mainstay in treating and preventing all types of acne lesions, it is better to learn how these products can be used with great success in darker-skinned patients than it is to avoid their use altogether and deny patients the clinical benefits they can offer.

Of all the topical retinoids available, tazarotene is often perceived as having the greatest irritation potential, and the author has therefore conducted a pilot study with this retinoid to demonstrate that topical retinoid therapy in general can offer both efficacy and freedom from pigmentation problems in darker-skinned patients with acne vulgaris.

### Table 1. Structural and functional differences and similarities between white skin and darker skin.

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<th>Similarities</th>
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<tr>
<td>Greater number of cell layers in stratum corneum in black skin6</td>
<td>Stratum corneum thickness5,16</td>
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<tr>
<td>Higher levels of spontaneous desquamation in black skin compared with white and Asian skin7</td>
<td>Sebaceous gland activity11</td>
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<tr>
<td>Lower levels of stratum corneum lipids in African American skin than in Caucasian or Hispano-American skin8</td>
<td>Corneocyte surface area2</td>
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**REFERENCES**

1. Data on file, Allergan, Inc.
2. Leyden J, Grove GL. Randomized facial tolerability studies comparing gel formulations of retinoids used to treat acne vulgaris. *Cutis.* 2001; 67 (suppl 6S) (In press).
**Pilot study**

A total of 14 patients with mild-to-moderate facial acne vulgaris were enrolled (10 African American and 4 Hispanic; 7 females and 7 males; mean age of 29 years). The skin phototype of all patients was V or VI. A 2-week washout period for all anti-acne medications and medicated cosmetic preparations was required prior to starting the study, with a 30-day washout period for oral contraceptives, oral antibiotics, systemic corticosteroids, and investigational drugs. Patients were requested to wash their face twice daily using Cetaphil® cleanser and, after the morning cleansing, to apply MD Forté® Total Daily Protective sunscreen. They were also asked to dilute a pea-sized amount of tazarotene 0.05% gel with Cetaphil® moisturizer (1:1) and to apply the diluted mixture to their face each evening 10–20 minutes after facial washing. If this was sufficiently well tolerated, they switched to using undiluted tazarotene 0.05% gel after 2 weeks of treatment. The total treatment time was 8 weeks and patients were evaluated for efficacy and tolerability at Weeks 4 and 8.

Of the 14 patients enrolled in the study, 10 completed. All discontinuations were due to non-compliance or loss to follow-up, and thus no patient discontinued due to irritation.

Among the completing patients, 5 were able to switch to the full strength tazarotene 0.05% gel after 2 weeks of therapy and 5 remained on the 1:1 diluted formulation.

Both the mean noninflammatory lesion count and the mean inflammatory lesion count showed significant reductions from baseline at Weeks 4 and 8 (Figures 1 and 2). There were no significant changes in the mean pigmented intensity of the patients’ skin. Furthermore, there was a general lack of skin irritation (no patients reported burning, and the levels of dryness, erythema, peeling, and pruritus did not significantly change from baseline), suggesting that such treatment does not predispose to irritation-induced hyperpigmentation. Interestingly, the perception of oiliness was significantly reduced from baseline at both visits.

The results of this pilot study demonstrate that, in darker-skinned patients, initial titration of topical retinoid therapy from a low dose can achieve marked improvements in acne that are well tolerated and do not predispose to irritation or hyperpigmentation (Figures 3 and 4). Although this study was performed with tazarotene, it is likely applicable to all topical retinoids. Further research is now warranted to confirm these findings in a larger patient population.

![Figure 1. Percentage reduction in mean noninflammatory lesion count (n = 10; baseline count = 8).](image1)

![Figure 2. Percentage reduction in mean inflammatory lesion count (n = 10; baseline count = 20).](image2)

* Galderma Laboratories, Inc. Fort Worth, Texas
† Allergan Inc., Irvine, California
REFERENCES


Further Reading Suggestions

The following information sources provide an opportunity to gain a broader perspective on some of the subject areas discussed in this publication.

**RETIROIDS**

**HYPERPIGMENTATION AND ACNE**

**TREATMENT OF SKIN PROBLEMS IN DANCER-SKINNED PATIENTS**

Self-Assessment Quiz

To obtain credit, complete the Self-Assessment Quiz below and Evaluation Form at the back of this publication. Participants must receive a passing score of 75% to receive a CME certificate. Please allow 3 to 4 weeks for certification of completion or other notification.

1. Why are topical retinoids effective against inflammatory acne as well as noninflammatory acne?
   a) They reduce the development of microcomedones
   b) They have both immunomodulatory activity (which reduces inflammatory lesions) and keratolytic activity (which reduces noninflammatory lesions)
   c) They have both potent bactericidal efficacy (which reduces inflammatory lesions) and keratolytic activity (which reduces noninflammatory lesions)
   d) They reduce sebum secretion, thus helping to prevent follicular blockage

2. The results from trials with tretinoin and tazarotene show that the earliest points at which both drugs achieve significantly greater reductions in lesion count than vehicle are:
   a) 2–4 weeks for noninflammatory lesions and 12 weeks for inflammatory lesions
   b) 6–8 weeks for both noninflammatory and inflammatory lesions
   c) 6–8 weeks for noninflammatory lesions and 12 weeks for inflammatory lesions
   d) 12 weeks for both noninflammatory and inflammatory lesions

3. Why is it important to initiate topical retinoid therapy early in the course of a patient’s acne?
   a) To help prevent scarring
   b) To prevent further lesional development
   c) Because topical retinoids take a few weeks to reach maximum efficacy
   d) All of the above
4. The studies described in this publication suggest that topical retinoid tolerability is influenced:
   a) More by the sensitivity of a person’s skin than by the individual retinoid
   b) More by the individual retinoid than by the sensitivity of a person’s skin
   c) More by the individual retinoid than by the vehicle of the formulation used
   d) More by the vehicle of the formulation used than by the sensitivity of a person’s skin

5. Which of the following is NOT thought to be one of the main physiological factors contributing to sensitivity of the skin?
   a) Low linoleic acid levels in the diet
   b) Vascular reactivity
   c) Difficulty downregulating inflammation
   d) Lack of integrity in the stratum corneum

6. Which of the following is likely to help optimize the tolerability of topical retinoid therapy?
   a) Using in conjunction with alpha-hydroxy acids
   b) Using a facial scrub
   c) Washing the face with soap
   d) Applying the retinoid sparingly

7. Which of the following is NOT likely to help optimize the tolerability of topical retinoid therapy?
   a) Liberal use of moisturizers
   b) Initiating therapy slowly and gently
   c) Initiating therapy in the perioral area
   d) Avoiding astringents

8. In which racial ethnic group is postinflammatory hyperpigmentation most likely to arise?
   a) Caucasians
   b) Japanese
   c) African Americans
   d) Chinese

9. Should the treatment of acne in darker-skinned patients differ from that in Caucasian patients and, if so, how?
   a) No – treatment does not need to be tailored to darker skin types
   b) Yes – oral antibiotics should be used more readily
   c) Yes – all potentially irritating medications, such as benzoyl peroxides and topical retinoids, should be avoided
   d) Yes – topical retinoids and other potentially irritating medications should still be first-line therapy but they should be titrated up from a low initial dose

10. Why are darker-skinned patients more likely to develop postinflammatory hyperpigmentation than Caucasian patients?
    a) They are more likely to experience allergic contact dermatitis
    b) They have higher levels of spontaneous desquamation
    c) They have less sebaceous gland activity
    d) Their melanocytes tend to overreact to cutaneous injury
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<td>Communicate with patients</td>
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</tr>
<tr>
<td>Manage my medical practice</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>Other ______________________</td>
<td>______________________</td>
</tr>
</tbody>
</table>

   ________________________________________________________________________________________
   ________________________________________________________________________________________
Please circle the correct answers:

1. a b c d
2. a b c d
3. a b c d
4. a b c d
5. a b c d
6. a b c d
7. a b c d
8. a b c d
9. a b c d
10. a b c d

Name: ______________________________________________________________________________________

Mailing Address: ___________________________________________________________________________
__________________________________________________________________________________________

City: __________________________________________ State: ______ Zip Code: ____________________

Business Phone: ( ) __________________________ Fax Number: ( ) ________________________

E-mail: __________________________________________________________________________________

Sex:   M __________ F __________ Date of Birth: __________________________

Graduate of: __________________________________ Year: __________ Highest Degree: ________

Employer: ____________________________________ Specialty/Profession: ______________

Number of hours spent in this educational activity (up to 1 hour) ______________________________

To obtain credit:
1. Read the journal supplement.
2. Answer the questions in the self-assessment quiz on the posttest answer sheet above.
3. Complete the registration form and the evaluation form.

4. Mail the Posttest Answer Sheet/Registration Form and Evaluation Form to: Center for Advanced Medical Education, 24 Arnett Avenue, Suite 105, Lambertville, NJ 08530; telephone (609) 397-4777; fax (609) 397-5177.

5. You will receive a certificate of completion or other notification in the mail within 3 to 4 weeks.
6. No registration payment is required to obtain credit.