

Topical Therapies for Psoriasis: Improving Management Strategies and Patient Adherence

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n Abstract

Psoriasis is a chronic disease that has a substantial effect on quality of life of patients and often needs long-term treatment. Topical treatments for psoriasis include corticosteroids, vitamin D derivatives, tazarotene, anthralin, tacrolimus, pimecrolimus, and newer formulations of tar. Although many of these treatments are effective, they must be prescribed appropriately and used consistently for a period of weeks to months before clinical evidence of improvement can be seen and patients perceive that the treatment is working. As such, medication dosage/schedule, choice of vehicle, and especially patient adherence to medication are key factors for a treatment to be effective. Addressing patient preferences about treatments and concerns about treatment-related toxicities and managing their expectations represent additional aspects of patient care. Therapies such as calcipotriene and betamethasone dipropionate (Cal/BD) fixed combination foam and new drugs and vehicles continuously enhance the treatment landscape for psoriasis. Because adherence to topical treatment can be a major difficulty, keeping the treatment regimen simple and using new and sophisticated treatment vehicles that are acceptable to patients can likely improve treatment outcomes.

Keywords

Allergy; corticosteroids; foam vehicle; medication adherence; psoriasis; topical therapy; vitamin D

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Disease Assessment and Classification

The first step in selecting treatment for an individual patient with psoriasis is physical evaluation of the disease to determine the type of lesions and severity of disease. Disease severity classifications

include the National Psoriasis Foundation Psoriasis Score (NPF-PS), Psoriasis Area Severity Index (PASI), and Investigator's Global Assessment (IGA)/Physician's Global Assessment (PGA). In addition to physical attributes of the disease, NPF criteria measure quality of life and also reflect the patient's perception of disease and symptoms, giving the clinician additional parameters to accurately determine how the disease is affecting the patient. The other two classification systems—PASI and IGA—do not consider patient-related parameters.

According to the NPF system (**Figure 1**), psoriasis is defined as mild (<3% body surface area [BSA] covered), moderate (3%-10% BSA), or severe (>10% BSA).¹

The IGA is primarily an evaluation of how the patient looks.² In this method, individual plaques are assessed and the average appearance is defined as severe (if thick and scaly with a lot of erythema), moderate (moderate in its scaling, thickness, and redness), mild, almost clear (perhaps still pink and barely perceptible without real scaling), and clear (completely clear without any erythema). This measure has no correlation with amount of disease but only determines the severity of the plaques. Throughout treatment, the clinician (or investigator in the case of a clinical trial) monitors disease severity and how well the patient's plaques are progressing on the treatment.

Due to the different parameters used in these two independent systems of classification, unified patient evaluation and diagnosis of severity can be challenging for practitioners. For example, a patient with an affected area of only 2% BSA (defined as mild disease by NPF criteria) can be diagnosed as "severe" according to the IGA classification. Conversely, patients who have moderate to severe disease by the IGA system can be diagnosed with BSA >10%, and actually have severe disease by NPF assessment. Clinicians must

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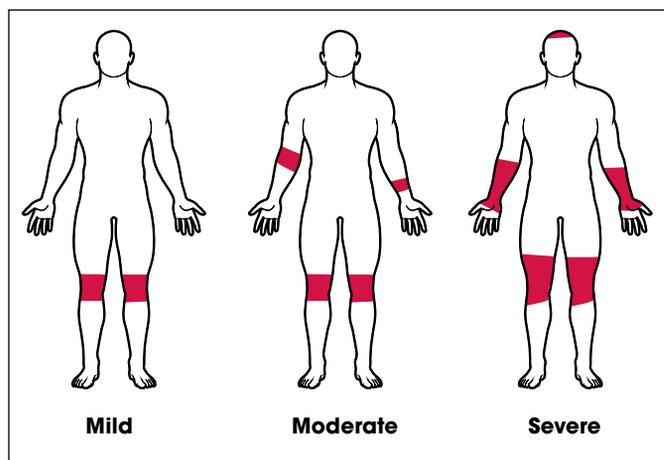


FIGURE 1. Classification of psoriasis according to the National Psoriasis Foundation.¹

remain aware of these differences when they are evaluating clinical trial data. They must read the protocol carefully and understand the methods of patient assessment. Usually, a “moderate to severe” disease designation in clinical trial data indicates an IGA severe status.

Topical Treatments for Psoriasis

Approximately 80% of patients with psoriasis have localized disease, which can be treated with topical therapies. As such, topical corticosteroids remain the mainstay of psoriasis treatment despite the development of newer therapies.³ However, some patients on systemic therapy will likely need simultaneous treatment with topical agents. This strategy may allow for minimizing prescribed doses of systemic medications, may provide additional symptom relief, and may even be psychologically comforting for some patients.⁴ In contrast to systemic medication, topical therapy can potentially avoid the side effects associated with systemic exposure to medications.⁵ Corticosteroids act via anti-inflammatory, anti-proliferative, and immunosuppressive pathways by affecting gene transcription. However, the exact mechanism of action of corticosteroids in psoriasis is not clearly understood.⁴

Topical agents rapidly improve symptoms⁶ and are frequently used as first-line therapy.⁷ Currently approved topical treatments include prescription medications such as corticosteroids (most commonly used alone or in combination therapy), vitamin D derivatives, vitamin A derivatives (tazarotene), and anthralin. The immunomodulators tacrolimus and pimecrolimus, which are currently not approved for psoriasis, are also used as topical therapy. Tar has been used historically, but patients do not favor it because of the odor and sticky formulation. Newer tar formulations in a liquid and foam are more cosmetically acceptable.

How Effective Are Topical Therapies?

Evidence-based ranking used in clinical guideline recommendations and vasoconstrictor studies that correlate with drug efficacy are two methods by which the potency and efficacy of topical drugs are established.

Strength of recommendations

A work group of psoriasis experts led by Alan Menter, MD,^{8,9} reviewed evidence-based data to create a unified ranking system for available topical therapies for psoriasis and to develop clinical recommendations for psoriasis care guidelines. Medications were ranked as A (based on large, prospective, double-blind studies and consistent and good quality patient-oriented evidence), B (inconsistent or limited quality patient-oriented evidence), and C (based on consensus, opinion, or case studies). Topical therapies with a class A ranking are statistically superior to other topical therapies and include class I corticosteroids, vitamin D analogues, tazarotene, and combinations of either corticosteroids and vitamin D analogue, or corticosteroids and tazarotene.⁹

Vasoconstrictor studies

The classification of steroids is based on vasoconstrictor study data, which correlate with potency of the drug (Table 1).¹⁰⁻¹² The vasoconstrictor assay, which has most utility in clinical trials, uses pharmacodynamic measures, and provides quantifiable and objective data regarding the delivery of the drug through a skin barrier and the rate of clearance from the site of application.¹³

TABLE 1. Potency of Topical Steroids¹⁰⁻¹²

Class	Selected Preparation
I (ultra-high potency)	<ul style="list-style-type: none"> Augmented betamethasone dipropionate 0.05% ointment, gel, lotion Clobetasol propionate 0.05% cream, ointment, lotion, foam Fluocinonide 0.1% cream Desoximetasone 0.25% spray Halobetasol propionate 0.05% cream, ointment
II (high potency)	<ul style="list-style-type: none"> Augmented betamethasone dipropionate 0.05% cream Betamethasone dipropionate 0.05% cream, ointment, foam, solution Desoximetasone 0.25% cream, ointment Fluocinonide 0.05% cream, ointment Mometasone furoate 0.1% ointment
III (mid potency)	<ul style="list-style-type: none"> Fluticasone propionate 0.005% ointment Halcinonide 0.1% ointment Betamethasone dipropionate 0.05% emollient spray
IV	<ul style="list-style-type: none"> Mometasone furoate 0.1% cream Triamcinolone acetonide 0.1% cream, ointment
V	<ul style="list-style-type: none"> Fluocinolone acetonide 0.025% cream, ointment Hydrocortisone valerate 0.2% ointment
VI (low potency)	<ul style="list-style-type: none"> Desonide 0.05% cream, ointment, lotion, gel, foam Alclometasone dipropionate 0.05% cream, ointment
VII	<ul style="list-style-type: none"> Hydrocortisone 1% cream, ointment Hydrocortisone 2.5% cream, ointment

Factors That Affect Absorption of Topical Medications

Clinicians must consider several factors that can affect the rate at which topical medications are absorbed in the skin. Which anatomic site is being treated and how actively a drug enters the skin in that area is the first issue for efficacy. Factors such as skin condition (intact or broken/diseased with abnormal barrier), hydration, and occlusion are important criteria for characterizing topical medications because they can affect absorption into the skin and consequently affect efficacy. When treating children, clinicians must remain aware that newborns have a much higher surface area-to-weight ratio and therefore have much higher systemic absorption from topical medications.¹⁴

Penetration into the skin increases when the skin is disrupted or excoriated, well hydrated (such as after a shower), or occluded—either by applying a wrap after the medication is applied or due to natural occlusion caused by skin folds in areas such as under arms, under the breasts, and the groin.

The anatomic site and associated BSA is another factor that can influence absorption. With a higher BSA, drug entry into the skin is increased. Therefore, percutaneous absorption (calculated as the ratio of total absorption for each anatomic site compared to the forearm [estimated by the amount of 14C-hydrocortisone excreted in the urine]) is significantly different across various body areas. For example, absorption in the forearm is 1, compared with 0.83 for the palm, 3.5 for the scalp, which is one of the most difficult areas to treat, and 42 for the scrotum, which is the highest of all sites.^{15,16} Clinicians must be exceptionally careful when they are using medication on the scrotum because potentially high levels of medication can be introduced systemically.

In addition to BSA, the type of vehicle can affect absorption as well. Clinicians should note that certain body areas are better platforms for one vehicle than the other.¹⁷ Ointments work best on palms and soles, creams on flexural and genital areas, and lotions and shampoos on the scalp. Clinicians may favor minimizing absorption at the application site so that the medication remains over the diseased area for a longer time.

Vehicles for Topical Medications

Selection of drug delivery mechanism (either dermal or transdermal) is based on the treatment objective. To be effective, topical agents must gain entry into the uppermost layer (stratum corneum) of the skin and then pass across several tissue layers. Vehicles can not only increase the cosmetic elegance of the topical drug, but importantly, they can have a significant impact on drug efficacy and potency. Improved drug efficacy can be achieved only when the drug is in a formulation, or as a solute in a solvent or vehicle. The type of vehicle for a medication largely controls entry of the drug into the skin, and therefore the choice of vehicle can significantly affect medication efficacy.⁵

Vehicles must allow release of the drug and should be nonirritating, nonallergenic, and cosmetically acceptable. Traditionally, lotions, creams, ointments, gels, sprays, and powders have been used as vehicles for topical corticosteroids. Notably, new, refined vehicles such as foam allow better penetration than some ointments.

One study compared penetration of clobetasol propionate (CP) via a foam vehicle with that of the solution, cream, emollient cream,

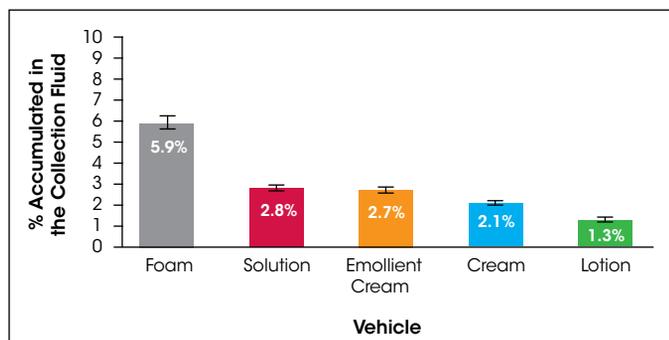


FIGURE 2. Percentage of applied drug accumulated in collection fluid at 12 hours.⁵

TABLE 2. Potency of Topical Steroids Changes With the Vehicle¹⁰⁻¹²

Class	Selected Preparation
I (ultra-high potency)	• Desoximetasone 0.25% spray
II (high potency)	• Desoximetasone 0.25% cream, ointment • Mometasone furoate 0.1% ointment
III (mid potency)	• Betamethasone dipropionate 0.05% emollient spray
IV	• Mometasone furoate 0.1% cream

and lotion forms. The study found that foam had a much faster penetration into the skin than the other vehicles, and delivered more CP than the other formulations (**Figure 2**).⁵ Although ointment was not included in this study, it showed better penetration than some of the other vehicles but had less penetration than the foam vehicle. Foam is a cosmetically acceptable vehicle for patients, and several studies involving patients with psoriasis have shown that patients preferred the foam formulation over other treatments.^{5,18,19}

Vehicles affect treatment efficacy

Clinicians must recognize that changing the vehicle will change drug potency. For example, as noted in **Table 2**,¹⁰⁻¹² if a patient who is receiving mometasone ointment (class II, high potency) is switched to the cream form (class IV), the treatment will be less potent. Conversely, changing from desoximetasone cream or ointment (class II, high potency) to a spray formulation (class I, ultra-high potency) will increase the potency of the drug and the patient may receive more medication than planned.

Initially it was thought that using an occlusive, heavy vehicle would allow better penetration of the drug into the skin. However, clinical data have shown that newer vehicles without occlusive properties can provide better penetration of the skin than some of the ointments that are occlusive.

With improved vehicles becoming available, some of the newer vehicles not only allow the enhancement of efficacy, they promote better patient appreciation for the drug and improve patient acceptance and adherence.

Safety Considerations for Topical Corticosteroids

Excessive steroid absorption through skin can occur due to long-term use, occlusion, or when used on a large surface area. Despite good safety records, most potent topical steroids are associated with some side effects. Clinicians should anticipate and manage side effects such as epidermal atrophy, hypothalamic-pituitary-adrenal (HPA) axis suppression, effects on pregnancy, steroid allergy, and vehicle (for example, propylene glycol) allergy.

Epidermal atrophy

One of the side effects that should be considered with the use of corticosteroids is epidermal atrophy.²⁰ A systematic review of 13 published studies on psoriasis concluded that in patients who used topical corticosteroids for a period of 4 weeks to 1 year, the risk of

skin atrophy was seen in 0% to 5% of patients.²¹ Corticosteroids can decrease or even inhibit epidermal lipid synthesis, causing a leaky barrier and greater transepidermal water loss (TEWL). Skin atrophy is usually not a problem unless the medication is used continuously for weeks. Clinicians should treat inverse psoriasis with low-potency (class VI and VII) corticosteroids so that the risk of corticosteroid-induced cutaneous atrophy in the intertriginous areas is minimal.

Hypothalamic-pituitary-adrenal axis suppression

Approximately 30% of patients will have a laboratory abnormality of HPA axis suppression after corticosteroid use. One recent analysis of 22 randomized clinical trials of topical corticosteroids and psoriasis (selected from articles published between 1980 and 2011) revealed that short-term biological effects of topical steroids on the HPA axis were observed in several studies. However, none of the studies showed any evidence of clinically significant HPA axis suppression due to absorption of topical steroids.²¹ Similarly, a second review of topical steroid risk analysis concluded that topical corticosteroids are unlikely to be associated with clinical signs or symptoms of HPA axis suppression even with the occurrence of adrenal suppression. In a single clinical trial in which patients used twice the maximum recommended amount of clobetasol propionate continuously for up to 18 months, pathologic adrenal suppression was observed.²² These data emphasize that corticosteroids can provide efficacy without safety concerns when used within the current safety guidelines.

Safety in pregnancy

Topical corticosteroids are generally safe for use in pregnant women; however, potential side effects can occur in some women when certain potent and super-potent steroids are used. In one study, a large database (N=35,503) of pregnant women who had used prescribed topical corticosteroids from 85 days before their last menstrual period (LMP) to delivery or fetal death was compared with 48,630 unexposed women. No association was noted between the use of corticosteroids and orofacial cleft (including two subtypes—cleft lip ± palate and cleft palate alone), preterm delivery, and fetal death (including miscarriage and stillbirth). In contrast, potent or very potent topical corticosteroid use shortly before and during pregnancy was significantly associated with fetal growth restriction (adjusted relative risk, 2.08; 95% CI, 1.40-3.10) in a dose-response fashion. The authors emphasized that increased risk of fetal growth restriction should be considered when corticosteroids are prescribed to pregnant women, and appropriate obstetric care must be provided.²³

Topical medication allergies

Clinicians should anticipate possible allergies associated with topical corticosteroids as well as vehicles and caution patients to be alert for any allergy-related symptoms that may arise.

Steroids are classified as classes A through D (including D1 and D2) based on their structure, which correlates with allergy-causing potential across each class.^{24,25} For example, if a patient has an allergy to hydrocortisone (a class A drug), he or she is more likely to have an allergy to all class A drugs, which have the highest allergy potential among all classes. In addition, the patient may have a cross-reaction to drugs in class D2. The least allergenic class is C, which includes desoximetasone in various potencies. Steroid allergy is extremely difficult to recognize. If clinicians are concerned about

steroid allergies, using a class C drug will minimize that potential risk. Comprehensive patch testing to all active and inactive steroid ingredients should be performed.

Clinicians should note that the overall prevalence of propylene glycol allergy in the United States is 2.9%, and all generic clobetasol ointments on the US market contain propylene glycol. In contrast, the prevalence of allergy for clobetasol (a class D steroid) is 0.8%. Desoximetasone ointment (available in 0.25% and 0.05% concentrations) can be considered for patients with allergy risks because this drug has no vehicle allergens. Prevalence of contact allergy is typically much higher in patients with chronic stasis dermatitis or ulcers. Allergy to the active molecule or the vehicle should be suspected in all patients who do not respond as expected to topical steroids.

In summary, potency and efficacy, application on appropriate skin areas, efficient and cosmetically acceptable vehicles, and limited side effects are key considerations for ideal topical treatments for psoriasis.

Vitamin D for Psoriasis Treatment

Efficacy of vitamin D

Traditionally, vitamin D has been a major player in the treatment of psoriasis. The synthetic vitamin D product calcipotriene was approved for use in the United States in 1994. The naturally occurring active form of vitamin D₃, calcitriol, was approved by the US Food and Drug Administration (FDA) in 2009 in an ointment formulation. Vitamin D analogues are used as a treatment for psoriasis, as monotherapy or in combination with topical corticosteroids.²⁶ Overall they restore healthy structure and function of the skin and have been found to be effective in treating psoriasis symptoms. Vitamin D reverses cellular changes that occur in psoriasis—such as lack of normal cell differentiation and destruction of the granular layer. It slows down this process by inhibiting keratinocyte proliferation, inducing differentiation, and reducing inflammation. The effect of vitamin D on the immune system is particularly relevant to dermatologists since it has implications for psoriasis and other skin conditions such as atopic dermatitis and skin cancer.²⁷

The side effect profile of vitamin D is mild; however, clinicians must recognize that calcitriol can interact with other factors and can be degraded by an acidic environment and ultraviolet (UV) light from the sun. Therefore, patients must be alerted about avoiding the sun when they are using topical calcitriol. Narrow-band UVA leads to maximum (almost 100%) degradation, whereas broadband UVB and UVA light cause less degradation of calcitriol.²⁸

Advantages of using topical vitamin D

Vitamin D₃ minimizes the risk of atrophy when used in conjunction with topical steroids. Topical steroids compromise permeability barrier and stratum corneum integrity by global inhibition of lipid synthesis. Calcitriol restores epidermal lipid synthesis and thus minimizes the effect of topical steroids.

In one study with hairless mice that examined the effect of calcitriol on epidermal permeability, topical calcitriol or the control vehicle was applied to each flank 20 minutes after treatment with topical clobetasol propionate. This treatment was repeated twice a day for 3.5 days. Assessment of barrier function was performed by several methods, including electron microscopy and immunohistochemistry. These results demonstrated that skin treated with calcitriol showed barrier recovery and an improvement in stratum corneum integrity compared with the control.²⁶

Monotherapy with vitamin D for difficult-to-treat areas

Vitamin D₃ monotherapy can be a treatment of choice when patients have inverse psoriasis—in areas where there are skin folds, such as the armpits, groin, and under the breasts. One bilateral study compared the safety and efficacy of two vitamin D preparations—calcitriol 3 µg g⁻¹ ointment and calcipotriol 50 µg g⁻¹ ointment in patients with psoriasis. Although both treatments were effective, IGA assessment of improvement from baseline showed greater control of calcitriol-treated lesions than the calcipotriol-treated areas (*P*<0.02).²⁹

Choice of vehicle affects topical vitamin D treatment

As in the case of corticosteroids, the choice of vehicle affects the efficacy of topical vitamin D treatment. For example, calcipotriene ointment provides better penetration and better efficacy; however, it also causes considerable irritation. Many patients prefer the cream vehicle; however, efficacy is significantly decreased with the cream, and it is associated with skin irritation similar to the ointment. Vitamin D solution has a modest effect on the scalp; however, it also causes less irritation than the ointment (Table 3).

Other treatment options for sensitive areas include topical immunomodulators such as tacrolimus or pimecrolimus, which are currently not FDA approved for psoriasis.

Combination Therapy With Topical Corticosteroids and Topical Vitamin D

The first trials of combining topical steroids and topical vitamin D were conducted in the 1990s. Lebowhl and colleagues³⁰ compared the use of halobetasol ointment (once-daily super-potent steroid) and once-daily vitamin D ointment with super-potent topical steroids twice a day and vitamin D twice a day (Figure 3). They found that by using each product once a day, not only were patients able to obtain better efficacy compared with topical steroids alone twice a day, but use of potent steroids could be reduced by half. When patients are prescribed more than one drug and are given detailed instructions on how to use these medications at the recommended sequence and frequency, it can be challenging for some patients.³⁰

Based on these data, the concept of topical combination therapies emerged. However, one concern with vitamin D was that it would interact with other components of therapy. Second, combining two drugs would dilute the effective concentration of each component by half. Third, combination of two separate vehicles would create a larger vehicle, and absorption into the skin could be affected. To

TABLE 3. Effect of Vehicle on Calcipotriene Efficacy

Vehicle	Marked Improvement (%)	Clear (%)	Skin Irritation (%)
Ointment	70	11	10-15
Cream	50	4	10-15
Solution	31	14	1-5
Foam	41 (almost clear scalp)	14-27 (almost clear body)	2

Table courtesy of Linda F. Stein Gold, MD.

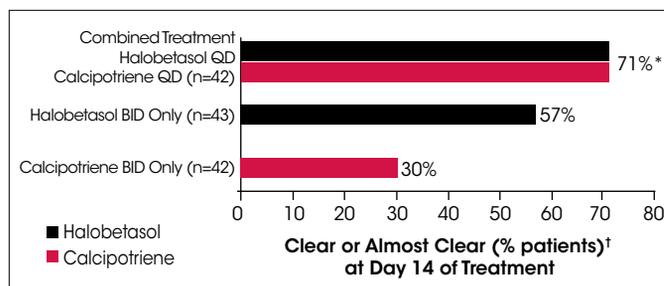


FIGURE 3. Genesis of combination therapy.³⁰

**P*<0.001 vs calcipotriene.

†Mean global assessment.

BID=twice a day; QD=every day.

overcome these challenges, through sophisticated vehicle technologies, a fixed combination of calcipotriene (dissolved in an anhydrous environment) and betamethasone dipropionate (micronized and suspended in the vehicle) (Cal/BD) was developed that allowed each of the active ingredients to stabilize in the combined environment. Once-daily application of Cal/BD was statistically superior to each of the individual ingredients as early as week 1. At 4 weeks there was a 71.3% reduction in mean PASI score.³¹

A suspension of the Cal/BD combination, which was more cosmetically elegant, was developed. The suspension was more versatile because it could potentially be used on the body and the scalp, thus reducing the complexity of the treatment regimen. However, although this formulation was efficient, a response could be seen only after 8 weeks.³²

Calcipotriol + betamethasone fixed combination foam

After the success of Cal/BD ointment, this combination was explored in a new vehicle—a more cosmetically elegant aerosolized foam. The foam vehicle is an oil and paraffin-based formulation, which is partly dissolved in a mixture of propellants (dimethyl ether and butane). The foam is alcohol free and enhances skin penetration of calcipotriene and BD.³³ Preliminary penetration studies performed on minipig skin showed greater penetration by the foam formulation than by the ointment (Figure 4).³³ Thus, changing the vehicle from ointment to aerosolized foam enhanced the efficacy of the combination treatment.

Two issues to be considered with increased penetration were medication safety and correlation of the drug with efficacy. These issues

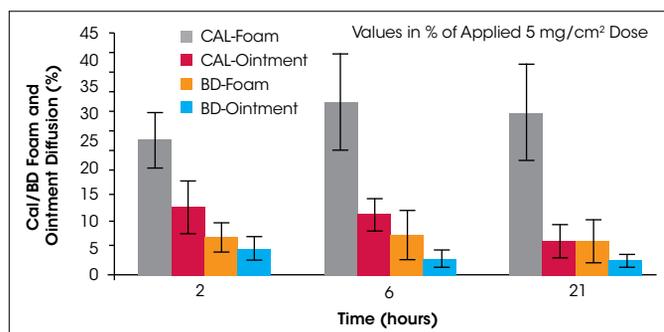


FIGURE 4. In vitro minipig skin penetration data for calcipotriol in cal/BD ointment or Cal/BD aerosol foam formulation.³³ AF=aerosol foam; BD=betamethasone dipropionate, 0.5 mg/g; Cal=calcipotriol, 50 mg/g.



FIGURE 5. Improvement in target lesion severity over time; representative images from a study patient using once-daily Cal/BD aerosol foam at baseline (A), week 1 (B), and week 4.³⁵ Used with permission. BD=betamethesone dipropionate, 0.064%; Cal=calcipotriene, 0.005%.

were examined by comparing the ointment and foam forms of Cal/BD fixed combination in a vasoconstrictor study. The foam formulation showed stronger vasoconstrictor effects, indicating a possibly more potent formulation.

Safety of Cal/BD

The phase II Maximal Use Systemic Exposure (MUSE) trial examined the safety of Cal/BD fixed combination foam.³⁴ Thirty-five patients with a BSA of 15%-30% were treated with the medication at a mean dose of 62 g/wk, which was approximately twice the dose of that used in phase III clinical trials. None of the patients showed HPA axis suppression, as indicated by a 30-minute post-stimulation cortisol level ≤ 18 mcg/dL at day 28. In addition, there was no evidence of an effect of Cal/BD aerosol foam on calcium homeostasis, based on evaluation of serum and 24-hour urinary calcium parameters. There were no unexpected adverse events.

Efficacy of Cal/BD

A double-blind, randomized, 4-week, vehicle-controlled phase III trial, Cal/BD foam in PSoriasis vulgaris, a Four-week, vehicle-controlled efficacy And Safety Trial (PSO FAST), examined the efficacy of Cal/BD fixed combination foam. Patients (N=426, aged 18-87 years) with mild to severe plaque psoriasis were randomized 3:1 to receive either Cal/BD foam or vehicle once a day.³⁵ Primary efficacy endpoints at week 4 were clear or almost clear with at least a two-grade improvement.

At 2 weeks, 26% of patients were clear or almost clear. At week 4, more than half (53.3% vs 4.8%; odds ratios [OR], 30.3; 95% CI, 9.7-94.3) of patients were clear or almost clear with the therapy (Figure 5).³⁵ In terms of adverse events, no new safety signals were found in this study.

In a separate head-to-head, four-arm, phase II efficacy and safety study, the Cal/BD aerosolized foam was directly compared with the active ointment form.³⁶ Patients (N=376) with 2%-30% BSA, and PGA of at least mild severity were randomized in a 3:1:3:1 ratio to receive once-daily treatment for 4 weeks of Cal/BD aerosol foam, Cal/BD vehicle, Cal/BD ointment, or ointment vehicle. The primary efficacy endpoint was the percentage of patients who achieved treatment success (clear or almost clear with at least a two-step improvement) at week 4 according to the PGA of disease severity. At week 4, a significantly larger proportion of patients using Cal/BD aerosol foam achieved treatment success compared with those using Cal/BD ointment (54.6% vs 43.0%) (Figure 6).³⁶ The number of adverse events was low (Table 4).³⁶ Based on the

efficacy and safety studies, Cal/BD foam was approved by the FDA for treatment of psoriasis.³⁷

Tazarotene

Tazarotene, a third-generation prescription topical retinoid, is available in 0.1% and 0.05% cream and gel forms. In clinical trials, tazarotene monotherapy has been found to be effective. When combined with a potent topical corticosteroid, the efficacy is improved and local irritation can be reduced. In a key study conducted in the late 1990s, at weeks 2, 8, and 12, tazarotene 0.1% gel in combination with a mid-potency corticosteroid and tazarotene plus a high-potency corticosteroid produced significantly higher treatment success rates than tazarotene with placebo cream (Figure 7).³⁸

Tazarotene has a pregnancy category X designation. A patient issue with tazarotene monotherapy is irritation at the site of application, which can result in patient nonadherence. Side effects have been reported in 10%-30% of patients and include pruritus, burning/stinging, erythema, worsening of psoriasis, irritation, and skin pain.³⁹

Tar

Treatment with tar and phototherapy (Goeckerman therapy) was the gold standard for treatment of psoriasis in the 1920s. Treatment response with topical application of tar was durable, with 90% of patients remaining clear for up to 8 months. Tar is exceptionally effective, with 90% clearing achieved in an average of 18 days.^{40,41} However, due to its unpleasant properties (dark color, sticky feel, odor, and the propensity to stain skin and clothes) it has not been a popular option with patients.

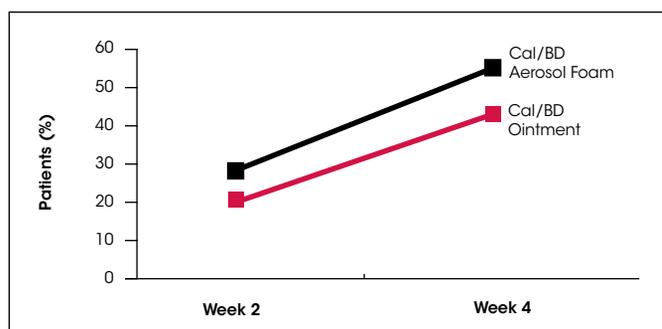


FIGURE 6. Proportion of patients achieving PGA-assessed treatment success over time.³⁶

BD=betamethesone dipropionate 0.064%; Cal=calcipotriene, 0.005%; PGA=Physician's Global Assessment.

TABLE 4. Adverse Events in the Cal/BD Aerosolized Foam Study³⁶

	Cal/BD Aerosol Foam	Cal/BD Ointment	Cal/BD Vehicle	Ointment Vehicle
Number of patients	141	134	49	51
Total number of AEs	20	23	2	2
Number (%) of patients reporting				
AEs*	16 (11.3)	14 (10.4)	1 (2.0)	2 (3.9)
SAEs†	0 (0.0)	2 (1.5) [†]	0 (0.0)	0 (0.0)
ADRs	1 (0.7)	4 (3.0)	0 (0.0)	0 (0.0)
Withdrawals due to unacceptable AEs	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)

*Most AEs were mild and only five were judged as probably or possibly related to treatment. The most common AEs were infections or infestations followed by gastrointestinal disorders.

†Two patients reported three SAEs: bile duct stone, hypertension, and bronchitis.

ADRs=adverse drug reactions; AEs=adverse events; BD=betamethasone dipropionate 0.064%; Cal=calcipotriene, 0.005%; SAEs=serious adverse events.

Today, with newer vehicles that allow more cosmetically elegant formulations such as solution (2.3% tar) and foam (2% tar), there is renewed interest in using tar for treating psoriasis. Topical preparations such as shampoos, creams, and ointments can be used once daily. A commonly used tar formulation includes 2% or 3% crude coal tar in 0.1% cream applied twice daily to plaques. Tar has anti-proliferative properties; however, its exact mechanism of action is not known.⁴

One study compared the effect of tar versus tar + narrow-band UVB (NB-UVB) light in a split-body study and found that in 4 weeks, 75% improvement was significantly more common on areas that were administered tar + UVB compared with UVB alone.⁴²

A large study of patients with psoriasis and eczema (N=13,200) examined the safety of coal tar ointments. Median exposure to medication was 6 months (range, 1-300 months). This study found that coal tar did not increase the risk of nonskin malignancies (hazard ratio [HR], 0.92; 95% CI, 0.78-1.09) or the risk of skin cancer (HR, 1.09; 95% CI, 0.69-1.72).⁴³

Anthralin (Dithranol)

Topical anthralin has been used since 1916. It has an anti-hyperproliferative effect in the epidermis, on mitogen-induced T-lymphocyte proliferation, and on neutrophil chemotaxis. It accumulates in keratinocyte mitochondria and induces apoptosis.⁴⁴

It is indicated for mild to moderate psoriasis in an outpatient setting and for severe psoriasis, usually in an inpatient setting. It is contraindicated for unstable plaque psoriasis, pustular psoriasis, and erythrodermic psoriasis. Controlled trials are limited; however, available studies show anthralin is significantly better than placebo. Anthralin is most commonly used for short contact (20-30 minutes) treatment, starting at 1% concentration with increasing concentration as tolerated by the patient.

Immunomodulators

Although not approved by the FDA for psoriasis, tacrolimus (0.1%) and pimecrolimus (1%) are calcineurin inhibitors that are effective for facial and inverse psoriasis treatment. They are generally well tolerated.

A study that evaluated the efficacy and safety of pimecrolimus cream (1%) in the treatment of moderate to severe inverse psoriasis

found that at week 2, 54% of the patients in the pimecrolimus group vs 21% in the vehicle-only group had an IGA score of 0 or 1 (clear or almost clear; $P=0.0169$). By week 8, 71% of the pimecrolimus group had an IGA score of 0 or 1. By week 8, 82% of patients using pimecrolimus had completely controlled disease vs 41% of the vehicle group ($P=0.0007$).⁴⁵

Similarly, in a separate study, patients treated with 0.1% tacrolimus showed excellent “improvement” or “clearing” by PGA as early as day 8, which continued until day 57 (Figure 8).⁴⁶ The groin area showed decreased erythema and scaling over time.

In 2005, the FDA issued an alert about a possible link between these agents and lymphoma and skin cancer in children, and placed a black box warning in 2006 on the prescribing information.⁴

Medication Adherence: The Crucial Factor for Successful Treatment

In clinical practice, the efficacy of a topical corticosteroid is dependent on many factors, including skin type, plaque thickness, and the most important factor—patient adherence.

Managing Patient Expectations

The key factors for controlling psoriasis include medication efficacy, rapid onset of action, simple treatment schedule, ease of medication use, and few side effects. Cosmetic property of the medication is an additional and important consideration for patients. A major dif-

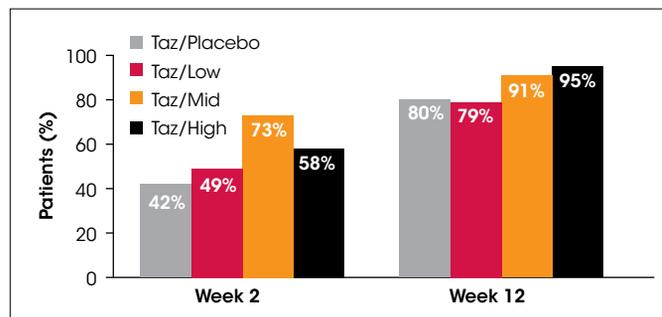
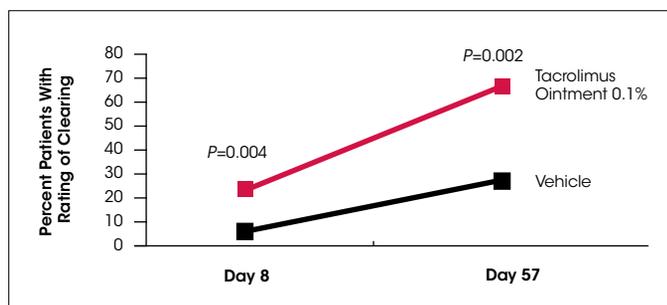


FIGURE 7. Topical tazarotene gel in combination with topical steroids.³⁸

* $P<0.05$ vs tazarotene 0.1% gel plus placebo cream.



■ **FIGURE 8.** Efficacy of tacrolimus.⁴⁶

difficulty with treatment success is that despite being given instructions for medication use, patients may have only superficial knowledge of the overall treatment strategy and may not be exactly aware of how to implement treatment. They may have inadequate knowledge of the disease and an inaccurate perception of efficacy and outcome time frame.

Counsel patients

Most patients would like to experience improvement in the first week. They may be discouraged from using the medication because in their view treatment effects are not visible quickly, and they may therefore believe that the treatment is ineffective. Clinicians must explain to their patients that they will experience reduced itching and redness relatively soon (for example, in 1-2 days); however, the full effects of treatment may be visible only after weeks. If patients realize the rationale for the treatment duration and the endpoint, they may be more willing to accept the treatment schedule.

Clinicians are in a key position to directly influence a patient's perception of psoriasis and to clearly explain the importance of continuing treatment. They should advise patients on why the treatment they have been prescribed would be effective and also which side effects they are likely to experience.

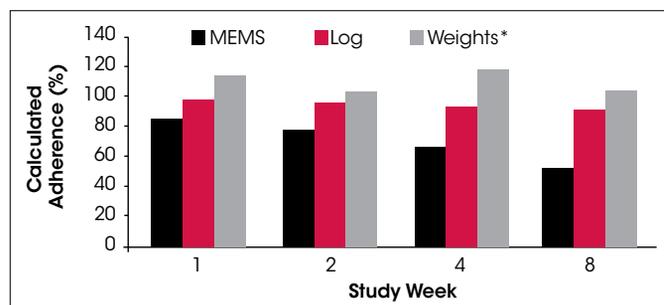
Encouraging Treatment Adherence

Despite the disease burden and major adverse impact on quality of life, patient adherence to psoriasis treatment is often poor. Patients may forget to take their medication, may find the treatment burdensome, may find the instructions for taking the medication long and confusing, or may take the medication only when they deem necessary.⁴⁷

Simplify the treatment schedule

Patients are more likely to follow treatment instructions effectively and adhere to treatment if the treatment schedule is simplified. If the treatment is complicated—for example, involves more than one topical medication—they may be confused because of the multiple steps/considerations involved: which treatment component should be used where (palm or scalp?) and at what time of the day (morning or evening?).

Clinicians must be cognizant of the fact that patients' reports about self-adherence to medications may not be accurate. In an 8-week trial, adherence to topical therapy was measured by electronic monitoring caps on medication containers, medication logs, and medication usage by weight. The authors found that adherence rates calculated based on medication logs and medication weights were consistently higher than those of the electronic monitors (**Figure 9**).⁴⁸



■ **FIGURE 9.** Patient reports do not mirror actual use.⁴⁸

MEMS=medication event monitoring system. *Weights of medication used by the patients.

Two additional studies examined self-reported adherence of patients with psoriasis. The first study compared self-reported adherence of patients who were given a salicylic acid and topical tacrolimus ointment and were instructed to apply this medication twice a day.⁴⁹ They were asked to keep a daily log of their medication use and were not informed that the medication dose they were taking was monitored by a medication event monitoring system (MEMS) in the cap.

In the second study, Feldman and colleagues⁵⁰ examined self-reported adherence of patients with psoriasis to topical medication. Patients were given a combination salicylic acid–0.1% tacrolimus ointment (or placebo) and were informed that they would be monitored on how they take their medications. They were instructed to apply the ointment twice a day and have follow-up visits at 1, 2, 4, and 8 weeks. It was not revealed to them that the medication containers included a cap with an electronic monitoring system that monitored the dose and time at which the medication was taken. This study found adherence rates decreased over time, but were significantly higher closer to the time of office visits ($P < 0.05$), indicating that there was a lack of consistent adherence.⁵⁰

Patients are usually willing to be medication adherent and will try multiple treatment options to find the optimal therapy that works for them. A simplified strategy, for example a once-daily dose, may be favorable to both patients and clinicians. As noted previously, new designer vehicles will likely reduce some of these issues.

In summary, patient adherence may be the largest barrier to treatment success with topical therapies. The most important reasons for lack of adherence are frustration with medication efficacy, time constraints and inconvenience, and fear of side effects. By understanding and modifying the factors that affect adherence to the topical treatment of psoriasis, improvement in patient adherence is possible and, therefore, better control of disease and patient outcomes is attainable.

Investigational Treatments

Several novel molecules and treatment approaches are being investigated for treatment of psoriasis. These include phosphodiesterase 4 (PDE4) inhibitor ointment, integrin inhibitor cream, Janus kinase (JAK)1/JAK2 inhibitor (ruxolitinib) cream, tyrosine kinase inhibitor cream and ointment, and dihydrofolate reductase inhibitor (methotrexate) proprietary vehicle.

Conclusions

Corticosteroids are the cornerstones of topical treatment for psoria-

sis, although they can cause potential side effects such as HPA axis suppression and dermal atrophy. Combination therapy with corticosteroids and vitamin D offers the advantage of minimizing side effects caused by both agents. Regardless of which medication is used, the choice of vehicle is of critical importance because in addition to providing cosmetic elegance, which can lead to improved patient perception and adherence to medication, the vehicle can enhance drug efficacy. Although used historically, topical retinoids still have a place in the treatment of psoriasis; ideally they should be used in combination with a potent topical steroid. As new molecules and sophisticated vehicles are developed, patients will have additional effective treatment options for psoriasis in the future.

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POST-TEST CME/CE QUESTIONS

Topical Therapies for Psoriasis: Improving Management Strategies and Patient Adherence Evaluation Form

Original Release Date: March 2016 • Most Recent Review Date: March 2016

Expiration Date: February 28, 2018 • Estimated Time to Complete Activity: 2.5 hours; 3.0 contact hours

To get instant CME credits online, go to <http://tinyurl.com/psoriasisistopicalsuppl16>. Upon successful completion of the online test and evaluation form, you will be directed to a Web page that will allow you to receive your certificate of credit via e-mail. Please add cmepd@louisville.edu to your e-mail "safe" list. If you have any questions or difficulties, please contact the **University of Louisville School of Medicine Continuing Medical Education (CME & PD)** office at cmepd@louisville.edu.

- 1. According to the National Psoriasis Foundation (NPF) system, psoriasis is considered moderate if it covers how much body surface area (BSA)?**
 - A. <3%
 - B. 3% to 10%
 - C. 11% to 15%
 - D. >15% to 20%
- 2. All of the following topical medications have a strength of recommendations designation of "A" except:**
 - A. Class I corticosteroids
 - B. Class II corticosteroids
 - C. Tazarotene
 - D. Combination corticosteroid and vitamin D analogue
- 3. The Investigator's Global Assessment evaluates psoriasis based on which of the following:**
 - A. Amount of body surface area affected
 - B. Severity of the plaques
 - C. Patient's perception of the disease
 - D. Family history
- 4. When a topical medication is applied for treating psoriasis, which anatomic site will have the highest absorption?**
 - A. Scrotum
 - B. Palm
 - C. Scalp
 - D. Forearm
- 5. Psoriasis treatment in the form of a lotion will work best on which areas?**
 - A. Scalp
 - B. Sole
 - C. Palm
 - D. Flexural
- 6. In addition to being nonirritating and nonallergenic, which of the following properties of a topical medication vehicle is likely the most important for encouraging patient adherence?**
 - A. Only a small amount of medication needs to be applied
 - B. It should be colorless
 - C. It is cosmetically acceptable
 - D. It has antiproliferative properties
- 7. All of the following statements are true about side effects associated with topical treatments for psoriasis except:**
 - A. Skin atrophy can be a problem when corticosteroids are used long-term
 - B. Clinicians should treat inverse psoriasis with low potency (class VI and VII) corticosteroids
 - C. Approximately 30% of patients will have hypothalamic-pituitary-adrenal axis suppression after corticosteroid use, which is usually not clinically significant
 - D. Corticosteroids can increase epidermal lipid synthesis
- 8. All of the following statements are true about vehicles except:**
 - A. Changing the vehicle may change the drug potency
 - B. Changing the vehicle will not change the drug potency
 - C. Vehicles without occlusive properties can provide better penetration of the skin
 - D. The type of delivery vehicle largely controls entry of the drug into the skin
- 9. All of the following statements are true about the topical calcineurin inhibitors (TCIs) tacrolimus and pimecrolimus except:**
 - A. They are approved by the FDA for psoriasis
 - B. They are effective for facial treatment
 - C. They are effective for inverse psoriasis
 - D. They are usually well tolerated
- 10. Which of the following strategies is likely the most effective for improving a patient's adherence to medication?**
 - A. Schedule a follow-up visit
 - B. Involve family members when counseling patients
 - C. Ask patients to keep a daily log
 - D. Simplify the treatment schedule

EVALUATION FORM

Topical Therapies for Psoriasis: Improving Management Strategies and Patient Adherence Evaluation Form

Original Release Date: March 2016 • **Most Recent Review Date:** March 2016

Expiration Date: February 28, 2018 • **Estimated Time to Complete Activity:** 2.5 hours; 3.0 contact hours

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few moments to complete this evaluation form. Your response will help ensure that future programs are informative and meet the educational needs of all participants. CME/CE credit letters and long-term credit retention information will only be issued upon completion of the post-test and evaluation online at: <http://tinyurl.com/psoriasisistopicalsuppl16>. If you do not feel confident that you can achieve the above objectives to some extent, please describe why not.

Please indicate your profession/background:

- MD/DO
 MSN/BSN/RN
 PA
 APN/NP
 PharmD/RPh
 Resident/Fellow
 Researcher
 Administrator
 Student
 Other; specify _____

LEARNING OBJECTIVES: <i>Having completed this activity, you are better able to:</i>	Strongly Agree	Agree	Somewhat Agree	Disagree	Strongly Disagree
Interpret and evaluate emerging clinical trial data related to the use of new molecules and new formulations of topical treatments used in mild to moderate psoriasis.	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
Discuss topical treatments for psoriasis, including corticosteroids and nonsteroidal topical agents (such as those containing vitamin D, topical immunomodulators, and tar).	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
Explain the role of the vehicle in topical drug delivery and patient adherence.	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
Discuss four key issues—quantity of medication prescribed, vehicle type, adverse events, and allergic reactions—that can affect patients' acceptance and use of topical therapies.	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1

If you do not feel confident that you can achieve the above objectives to some extent, please describe why not.

If you anticipate changing one or more aspects of your practice/professional responsibilities as a result of your participation in this activity, please briefly describe how you plan to do so.

Based on the content of this activity, what will you do differently in the care of your patients/regarding your professional responsibilities? (check one)

- Implement a change in my practice/workplace.
 Seek additional information on this topic.
 Do nothing differently. Current practice/job responsibilities reflect activity recommendations.
 Do nothing differently as the content was not convincing.
 Do nothing differently. System barriers prevent me from changing my practice/workplace.

If you plan to change your practice/workplace, may we contact you in 2 months to see how you are progressing?

- Yes. E-mail address: _____
 No. I don't plan to make a change.

If you are not able to effectively implement what you learned in this activity, please tell us what the system barriers are (eg, institutional systems, lack of resources, etc)?

OVERALL EVALUATION:	Strongly Agree	Agree	Somewhat Agree	Disagree	Strongly Disagree
The information presented increased my awareness/understanding of the subject.	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
The information presented will influence how I practice/do my job.	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
The information presented will help me improve patient care/my job performance.	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
The program was educationally sound and scientifically balanced.	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
Overall, the program met my expectations.	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
I would recommend this program to my colleagues.	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
Linda F. Stein Gold, MD:					
Author demonstrated current knowledge of the topic.	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
Author was organized in the written materials.	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1

What topics do you want to hear more about, and what issue(s) regarding your practice/professional responsibilities will they address?

Please provide additional comments pertaining to this activity and any suggestions for improvement.
