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Editor-in-Chief: Dr Stuart Maddin

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EDITOR-IN-CHIEF

Dr. Stuart Maddin, Chairman of SkinCareGuide, is one of North America's leading dermatologists, and is the author of



numerous dermatologic journal articles, monographs and textbooks. In addition to providing consultative input to a number of pharmaceutical and biotech companies, he is the director of the clinical trials unit at the Department of Dermatology and Skin Science, University of British Columbia. Dr. Maddin has also acted in an advisory capacity to a number of drug regulatory agencies, such as the Health Protection Branch (Ottawa), the AAD-FDA Liaison Committee, and WHO (Geneva). He is the founder of the Dermatology Update symposia, now in its 24th year. As well, he is Past President of the Canadian Dermatology Association and served as Secretary-General of the International Committee of Dermatology — International League of Dermatological Societies.

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FAMILY PHYSICIAN ADVISOR

Dr. Lauren Yee is a family practitioner with a special interest in general dermatology. She is particularly interested in the areas of acne and atopic dermatitis, and has been conducting numerous dermatological clinical studies since 2000. Dr. Yee is a graduate of the University of Toronto and has a thriving solo medical practice located in Windsor, Ontario, which she established in 1990.

**Take our new
Dermatologic Diagnostic Challenge
on Page 8!**

Natural Topical Retinoids with Emphasis on Tretinoin for the Treatment of Acne

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Background

Microcomedones are the precursors to all acne lesions. Topical therapies, such as retinoids, have the ability to substantially reduce their number, thereby disrupting the pathways that lead to the development of both inflammatory and noninflammatory acne lesions.

Retinoids naturally occur in the human body and are implicated in the regulation of a variety of physiologic processes. Their mechanism of action can be explained by their interaction with cell receptors. This cellular interactivity, as it relates to acne, involves controlling and slowing the turnover of skin cells, reducing sebum secretion and inhibiting inflammatory responses. Retinoids can access the skin through systemic modes of administration, as well as through metabolism when applied topically. The effects of retinoids on epidermal proliferation, pigment maturation, and collagen production make them important for treating a number of skin conditions, and as such, they are used extensively.

Approved Topical Retinoids*Naturally occurring retinoids*

- All-trans retinol (used in over-the-counter cosmeceuticals)
- All-trans retinoic acid (tretinoin)
- Alitretinoin (US FDA approved for AIDS-related Kaposi's sarcoma)*

Synthesized retinoids

- Adapalene
- Tazarotene
- Bexarotene (US FDA approved for cutaneous lymphoma)*

* Not available in Canada

Histological Changes Following Prolonged Use of Topical Retinoids

- Epidermal thickening of atrophic skin
- Elimination of dystrophic keratinocytes, including actinic damaged cells
- Dispersal of melanin granules, such as those seen in sun damaged skin
- New dermal collagen formation
- Angiogenesis, which may be seen as telangiectasias
- Comedolysis, which breaks down comedones

Tretinoin

Tretinoin was introduced as the first topical retinoid in the 1970s. A number of products containing tretinoin have been developed since; each unique formulation incorporates specific bases and delivery systems, and includes claims of enhanced efficacy and reduced irritancy. Topical tretinoin is approved in various jurisdictions for the treatment of acne, well as for photodamage and anti-aging.

Mechanism of Action

- Activates DNA, normalizing gene expression, affecting cell differentiation and keratinization of the follicular epithelium, preventing comedone production, and triggering the lysis of existing comedones.
- Affects cell growth and differentiation, thereby providing the potential for this agent to improve fine lines, wrinkles, mottled pigmentation and skin roughness. Topical tretinoin has been shown to increase procollagen1 production, which plumps up the epidermis in those with depressed scars and wrinkles.
- Inhibition of the toll-like receptor 2 receptors, which are activated by *P. acnes*, may explain the significant anti-inflammatory effects seen in acne.
- Tretinoin, unlike systemic isotretinoin, does not have a direct effect on the sebum production.

Pharmacology

Only 1%-2% is absorbed in normal skin. However, absorption may be 15 times greater if dermatitis is present. There is minimal uptake into the dermis.

- Tretinoin is an active metabolite that does not require conversion.
- It is found normally in plasma.
- It is excreted in the hepatic system, as well as removed by skin desquamation.

Approved Indications for Use

- Acne
- Photoaging

Contraindications

- Nursing
- Pregnancy, at risk Category C, is a relative contraindication. Despite five case reports, there is no clear evidence that topical retinoids are harmful to the fetus. However, it is prudent to avoid, especially in the first trimester.

Precautions

- Exercise care when using with other photosensitizing drugs, e.g., tetracyclines and thiazides.
- Tretinoin can cause photosensitivity. Instruct patients to avoid unnecessary or prolonged exposure to sunlight, and wear sunscreen and protective clothing.
- Tretinoin can also cause skin irritation and hypo- or hyperpigmentation.

Patient Compliance Can Be Influenced by Product Selection

Skin irritation is a significant concern, especially for eczematous patients, whose skin is already hypersensitive from existing topical treatments; and further exacerbation by retinoids is not likely to gain compliance. Minimize irritation by selecting a tretinoin formulation that is combined with a vehicle most suitable for the patient's skin type. A special microsphere water-based gel delivery system where the tretinoin is delivered to the epidermis more slowly and evenly can be less irritating. This delivery system also allows more predictable sustained applications to be used in the skin. These new water-based gels must be distinguished from alcohol-based gels.

Patient Compliance Can Be Influenced by Product Selection (continued)

Other options to improve tolerance for other bases include:

- Using a cream base rather than an alcohol-based gel.
- Initially using a lower concentration of the retinoid.
- For those with oily skin, an aqueous gel might reduce an oily appearance.
- Patients with dry skin, do better by avoiding the traditional alcohol gels.

In the initial phase of treatment, it must be made clear to the patient that the acne can increase or appear to worsen. This perception is common even if there is an actual reduction in acne counts. Visible improvement may be noted after 2 weeks of treatment, but the appearance may be worse for the first few weeks. However, it is important for the sake of compliance to explain that significant improvement may take up to 2–3 months to occur.

Advice to the Patient to Enhance Compliance

- *Quantity:* Applying a small amount of the topical medication, i.e., about the size of a pea to form a thin, almost imperceptible layer, may reduce irritation.
- *Use a moisturizer:* Areas such as the nasolabial folds, as well as those below the corners of the mouth, are more easily irritated. Adding a noncomedogenic moisturizer before or after the application can reduce irritation.
- *Dry skin:* Applying tretinoin to dry, nonmoistened skin is advised. If irritation continues to be a problem, apply tretinoin to an unwashed face; this allows the skin's protective oils to build.
- *Time of application:* Some dermatologists recommend that anti-acne products with the potential to irritate should be applied in the early evening to avoid the occlusive effect of the sleeping face on the pillow.
- *Contact time:* Reducing contact time by washing the topical off with a gentle cleanser a few minutes after application may also reduce irritation. Contact time can be gradually increased as tolerated. When using the microsphere technology, this strategy may not be as relevant because the tretinoin is released more slowly onto the skin.
- *Frequency of application:* Initially, the application of the retinoid every 2–3 days will reduce irritation.
- *Area of application:* It is important that the retinoid be applied not just on individual spots, but all over the affected area to prevent the formation of new lesions.
- *Expectations for rate of response:* It must be made clear to the patient that the acne can increase or look as if it is increasing over the first few weeks. This perception is common even when the actual acne counts are reducing. For the sake of continued compliance the patient must understand that significant improvement may take 2–3 months to be seen, and it may take up to 6 months to see maximum benefit.
- *How long is treatment required?* Acne is a chronic condition so the patient must understand that long-term treatment is required, even after improvement has been achieved. Microcomedones are the first events occurring in acne formation and these invisible lesions can be prevented by continued topical retinoid use.
- *Photoprotection:* Sun avoidance or sun protection must be encouraged as tretinoin thins the stratum corneum, and allows greater entry of UV light into the skin.

Benefits

All acne patients can benefit from topical retinoids:

- As a first-line treatment for those with comedonal acne
- Mixed comedonal and inflammatory acne will benefit
- For mild-to-moderate inflammatory acne

Patients with severe acne can be helped by topical tretinoin once the severity of the acne has been diminished by systemic therapy. It can be used to reduce recurrence. Cystic acne needs systemic therapy, but topical retinoids, following the use of oral isotretinoin, may reduce recurrences by preventing the formation of microcomedones, as well as using the collagen enhancing properties to hasten the repair of depressed areas of the skin.

Conclusion

Topical retinoids are the cornerstone of acne therapy and they can be used across the entire spectrum of acne severity. Selecting the most suitable retinoid formulation, as well as dispensing proper advice in terms of drug application, can improve patient compliance. It is also important to establish realistic patient expectations with regard to the rate of improvement in order to ensure compliance and increase the chances of achieving treatment success.

Topical Antipsoriatic Treatments in 2007

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Background

The number of patients with psoriasis is increasing, while the number of medical dermatologists is shrinking. There are more than 1 million psoriasis patients in Canada, with 620,000 visits to a health care professional in 2006 for treatment of this condition. Approximately 35% of these visits were with dermatologists; the remainder was handled primarily by family practitioners.

Disease Severity

There are a wide range of definitions of disease severity for psoriasis. In light of the various measures that are currently available, patients can be separated into two categories: those treated with local (topical) therapy and those treated with systemic therapy. This article will deal with topical therapy.

Topical Treatment Options and the Treatment Triangle

Topical medications, either as monotherapy or in combination, are the most commonly prescribed treatments by both dermatologists and family practitioners. The treatment triangle brings together evidence-based medicine, patient preference, and the physician's expertise in order to determine the most appropriate treatment approach. Given the increasingly limited access to dermatologists, adequate education on all available treatment options must be provided to family practitioners in order for them to adequately manage the psoriatic population in Canada.

Commonly Used Topical Antipsoriatic Therapies

- Emollients/ Keratolytics
- Topical Steroids
- Tars
- Anthralin
- Tazarotene
- Calcipotriol
- Calcipotriol + Betamethasone Dipropionate
- Calcineurin inhibitors

Emollients

The use of emollients improves the skin barrier function by restoring hydration and forming a protective layer that guards against infection and other irritants. Additional benefits include:

- improvement of itching
- removal of superficial scales, resulting in a smoother appearance to the skin
- improvement of penetration of other topical medications.

Topical Corticosteroids

Corticosteroids are potent compounds widely used for their anti-inflammatory, immunosuppressive and antiproliferative effects.

- Efficacy and safety have been confirmed when used as monotherapy in short-term courses and when given intermittently for more lengthy periods.
- Studies have shown improved efficacy when applied in the late afternoon or evening.

Tar

Tar slows the proliferation of skin cells and reduces inflammation, itching and scaling. While tar compounds are very effective for treating scalp psoriasis, they have several limitations:

- They are odiferous.
- They can irritate and stain.
- They can cause folliculitis.
- There is concern that they may be carcinogenic.

Anthralin

Anthralin reduces the rapid acceleration of skin growth, as seen in psoriasis.

- An effective treatment for mild-to-moderate disease, however, patients are slow to respond.
- Skin irritation and staining are common side-effects.
- Its availability is limited and is rarely used by outpatients.

Commonly Used Topical Antipsoriatic Therapies (continued)

Tazarotene

- It is a retinoid with the ability to mediate skin cell proliferation and differentiation
- It is mostly used in non-psoriasis indications
- It may cause irritation to psoriatic lesions
- Its effects can be enhanced when used in combination with topical corticosteroids, calcipotriol and phototherapy.

Calcipotriol

- A vitamin D analogue that acts to modulate both epidermal proliferation and differentiation.
- Twice daily application has been shown to be more effective than tar, short contact anthralin, and some corticosteroids.

Compounding

Use of calcipotriol in combination with steroids enhances efficacy. However, compounding should be used with caution. Ad hoc mixtures of calcipotriol plus steroids (including betamethasone dipropionate and betamethasone valerate) have been shown to be unstable. The valerate steroid activity disappeared within 24 hours, while the dipropionate steroid activity was more than one-third depleted after only 4 weeks.

Calcipotriol plus Betamethasone Dipropionate

- Available as a stable commercial preparation.
- Phase III trials involving more than 6,000 psoriasis patients have demonstrated clear or almost clear responses in 50% of those treated after 4 weeks of therapy.
- Reduction in Psoriasis Area and Severity Index (PASI)

score was consistent throughout the study population: approximately 40% after 1 week and 70% after 4 weeks. The PASI is a visual rating system that is determined by assessing the amount of body surface area affected by psoriasis, redness, thickness, and degree of scaling.

- Response rates were uniform across patients of differing age, sex, races, and baseline disease severity.
- Combination therapy with calcipotriol and betamethasone dipropionate can enhance the rate and degree of improvement for patients undergoing treatment with UVB, PUVA, methotrexate, cyclosporine, retinoids, or alefacept.
- The addition of calcipotriol and betamethasone dipropionate can have a dose sparing effect, reducing some of the side-effects produced by many antipsoriatic treatments.
- Many dermatologists agree that including calcipotriol and betamethasone dipropionate in combination therapy produces synergistic effects.
- Can be considered as first-line topical therapy due to once daily application, quick onset of action, and favorable safety and efficacy profiles over 52 weeks of “as needed” use.

Topical Calcineurin Inhibitors

- Calcineurin inhibitors are immunosuppressive agents that interfere with T-cell signaling and affect the body's inflammatory responses.
- Studies have indicated therapeutic benefits for psoriasis, especially on the face, and in the groin and skin folds.

Noncompliance and Nonadherence

Noncompliance or nonadherence to treatment can influence outcomes in all disease states. They unquestionably lower response to treatment, and this is of particular concern with topical medications. When the illness has the severity potential of psoriasis, physicians need to find treatment options that best suit each patient.

There is no reliable method to ensure or improve compliance in patients with psoriasis. Some clinical strategies to promote compliance include:

- encouraging patient feedback and input surrounding their treatment.
- selecting fast-acting topical therapies.
- selecting treatments that facilitate ease of use, i.e., once-daily dosing.
- referring patients to national organizations for support.

Conclusion

Advancements in topical antipsoriatic therapies have provided safer and more effective treatment options, especially when used in combination. Consequently, much research is underway to investigate novel treatment combinations for psoriasis in the hope that it will provide further enhancements in efficacy that will lead to improved patient compliance.

Dermatological Drug Use in Pregnancy

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Background

It is well known that the developing fetus can potentially be affected by any medication given to the mother. However, despite this, the use of medications during pregnancy is common and pregnant women often present for treatment of dermatological disease. A recent multinational survey indicated that 86% of women took an average of 2.9 medications during their pregnancy [Collaborative Group on Drug Use in Pregnancy. *Int J Gynaecol Obstet* 39(3):185-96 (1992 Nov)]

US FDA Pregnancy Categories

During the 1950s diethylstilbestrol and thalidomide use in early pregnancy both led to disastrous consequences for the exposed offspring, which were not causally linked for years. These events led to the development of the US FDA Pregnancy Categories (Table 1) that are assigned before a drug is released.

A	No fetal risk in controlled studies.
B	No risk to human fetus despite possible animal risk or no risks in animal studies, but human studies lacking.
C	Human risk cannot be ruled out. Animal studies may or may not show risk.
D	Evidence of risk to human fetus.
X	Contraindicated in pregnancy.

Table 1: US FDA pregnancy categories for drugs

Acne

Topical

- Preferred during pregnancy
- Topical erythromycin (category B), clindamycin (category B), and benzoyl peroxide (category C) are safe
- Avoid topical retinoids
 - Case reports of congenital malformations with tretinoin (category C)
 - Use of adapalene (category C) and tazarotene (category X) are also not recommended.

Systemic

- Tetracyclines (category D) are associated with deciduous tooth staining, decreased bony growth, and maternal liver toxicity when taken after the first trimester.
- Erythromycin (category B) use in early pregnancy may be associated with a higher risk of cardiovascular malformations.
- Oral isotretinoin (category X) is a well-known teratogen. However, it is safe for women to conceive 1 month after this medication is stopped.

Rosacea

Topical metronidazole and azelaic acid are both category B and considered safe to use during pregnancy.

Psoriasis

Topical

- Topical corticosteroids (category C) are widely used in pregnancy, although intrauterine growth retardation has been reported.
- Only 6% of calcipotriene ointment (category C) is absorbed through the skin and is likely safe for localized disease.

Phototherapy

- Broadband UVB is considered the safest therapy for extensive psoriasis.
- PUVA is a potential teratogen, but adverse outcomes have not been reported.

Systemic

- Methotrexate (category X)
 - Can be used in women of childbearing potential who are using effective contraception.
 - Pregnancy should be avoided for at least one ovulatory cycle following cessation of the drug.
- Acitretin (category X)
 - Should not be prescribed for women of childbearing potential.
- Cyclosporin (category C) does not appear to pose a major risk to the fetus based on relatively small numbers.

Biologics

- Limited data available.
- Alefacept (category B) and efalizumab (category C)
 - No evidence of teratogenicity in animal reproduction studies or in offspring of women who inadvertently became pregnant while taking either of these drugs
- Etanercept (category B)
- OTIS data [Chambers C, et al. *J Am Acad Dermatol* 56(2):38 (2007)]
 - 35 pregnancies with first TM exposure
 - 17 pregnancies have resulted in live births
- 3 congenital abnormalities - no consistent pattern
- Infliximab (category B)
 - Multiple reports of exposure during pregnancy in women receiving treatment for rheumatoid arthritis and Crohn's disease
 - Used intentionally during pregnancy for induction or maintenance of remission in Crohn's disease
 - No evidence of embryotoxicity, teratogenicity or increased fetal loss
 - Placental transfer documented.

Systemic Corticosteroids (category C)

- Have been associated with intrauterine growth retardation and a small increase in incidence of cleft lip with or without cleft palate with first trimester exposure.
- When needed, the benefits of short courses of oral corticosteroids appear to outweigh the fetal risks, especially when given beyond the first trimester.

Topical Calcineurin Inhibitors

- Tacrolimus and pimecrolimus (category C)
- Oral tacrolimus has not been associated with fetal loss or teratogenicity.
- To date there are no reports of adverse effects on pregnancy with topical use of tacrolimus or pimecrolimus.

Antihistamines

- Chlorpheniramine and diphenhydramine (category B) are the antihistamines of choice for oral and parenteral use, respectively.
- One case-control study associated use of diphenhydramine with cleft palate in first trimester [Saxen I. *Lancet* 1(7854):407-8 (1974 Mar)]
- Linked to retrolental fibroplasia in premature infants when taken in last 2 weeks.

Antivirals

- Topical imiquimod (category B) is minimally absorbed and limited data has not shown adverse fetal effects.
- Podophyllin and podophyllotoxin (category C) have been associated with fetal abnormalities and deaths.
- Acyclovir, famciclovir and valacyclovir (category B) are probably safe.

Antifungals

- Topical antifungals are safe because of negligible percutaneous absorption.
- Minimal data for oral terbinafine (category B).
- Oral fluconazole (category C) 400 mg/d appears to be teratogenic.
 - Associated with a pattern of abnormalities involving the head and face, bones and heart.
- Smaller doses are likely safe.
- Itraconazole (category C)
 - No significant risk for major abnormalities.
 - Because of concern regarding the use of fluconazole, a structurally related triazole antifungal, avoidance of itraconazole is suggested in the first trimester.

Antibiotics (Systemic)

- Penicillins, cephalosporins, and azithromycin (category B) are generally considered safe in pregnancy.
- A large surveillance study observed a possible association between certain cephalosporins (cefactor, cefalexin, ceftriaxone, and cephadrine) and congenital malformation with first TM exposure.[Briggs GG, et al. *Drugs in Pregnancy and Lactation*. 7th ed. Philadelphia (PA): Lippincott Williams and Wilkins (2005).]

Conclusion

Medications that are considered safe in pregnancy are available for the treatment of common dermatological disorders. Knowledge of these medications is important when considering treatment options for both pregnant patients, and women of childbearing potential.

Dermatologic Diagnostic Challenge

Question: A 61 year old Caucasian male presents with chronic erythema of his cheeks and easy flushing. On questioning, he notes that he never gets any “bumps” on his face, but he occasionally gets styes on his eyelids. He has no problems with his blood pressure nor any history of diarrhea.

What is your diagnosis?

- Systemic lupus erythematosus
- Carcinoid syndrome
- Erythematotelangiectatic rosacea
- Periorificial dermatitis
- Papulopustular rosacea

Go online to www.SkinTherapyLetter.ca/cases
to view an image and learn the answer.

Case study submitted by Benjamin Barankin, MD, FRCPC

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EczemaGuide.ca	FungalGuide.ca	HerpesGuide.ca	Lice.ca
MildCleanser.ca	MohsSurgery.ca	PsoriasisGuide.ca	PsoriaticArthritisGuide.ca
RosaceaGuide.ca	SkinCancerGuide.ca	Sweating.ca	UnwantedFacialHair.ca

Medical professional sites:

SkinPharmacies.ca	SkinTherapyLetter.ca	Dermatologists.ca
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