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Topical Therapies for Psoriasis

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1. Introduction

Psoriasis is a chronic and recurring inflammatory condition of the skin that affects approximately 2% of the western population (Nestle et al., 2009). The most common form is plaque type psoriasis, the treatment of which is the focus of this chapter. Patients with psoriasis often present with scaly, painful and disfiguring skin lesions (Nestle et al., 2009). Although, it is seldom life-threatening, psoriasis is associated with a high degree of morbidity - patients are embarrassed about the appearance of their skin. There are significant psychosocial issues affecting these patients, often they experience social isolation, stigmatization, alcoholism and depression. In addition, patients with psoriasis, like those with other major medical disorders, have reduced levels of employment and income as well as a decreased quality of life (Horn et al., 2007). The combined costs of long-term therapy and social costs of the disease have a major impact on healthcare systems and on society in general. There are several co-morbidities that have been linked to psoriasis and it has been hypothesized that psoriasis as a disease has important systemic manifestations (Nestle et al., 2009). The shared conditions include the metabolic syndrome, depression, and cancer. Psoriasis can also occur in association with inflammatory bowel disease (Wolf et al., 2008), diabetes mellitus (Wolf et al., 2008) and HIV infection (Maurer, 2005). Although cases have been reported, it is unclear whether cancer particularly lymphoma and skin cancer, is related to psoriasis or the long term consequences of its treatment (Gelfand et al., 2006a). The relationship between psoriasis and the risk of cardiovascular disease is of emerging significance (Gelfand et al., 2006b). While patients with mild psoriasis appears to be in no excess risk, the moderate and severe form of the disease is associated with an increase in frequency of myocardial infarction and an increase in mortality, in large part because of cardiovascular events (Gelfand et al., 2006b). If confirmed, these findings would have major implications for future preventive and therapeutic strategies. Further, it is estimated that a significant population of juvenile guttate psoriasis cases are preceded by streptococcal infections (Campalani & Barker, 2005).

For treatment purposes, psoriasis can be categorized into localized and generalized forms, based upon body surface area (BSA) involvement. For localized, mild to moderate disease, usually defined as lesions covering <10% of body surface area, topical therapy is often
sufficient (Nestle et al., 2009). For generalized disease, systemic therapy approaches such as oral therapy, immunotherapy and UVB phototherapy are effective treatment options. In any case, the treatment plan should include obtaining rapid control of the disease and maintaining that control. In this chapter, the authors provide an overview of current guidelines for topical management of psoriasis, novel mono- and combination topical therapies as well as combination regimens of topical and phototherapy. Several of the well-established traditional topical medications such as coal tar, salicylic acid and anthralins are only briefly reviewed here. Interested readers are referred to the following references (Su & Fang, 2008; Witman 2001) for information. An overview of the topical antipsoriatic medications is summarized in Table 1. Most of the trade names used throughout this chapter represent those marketed in United States (US).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Disease Type</th>
</tr>
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<tbody>
<tr>
<td><strong>Corticosteroids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clobetasol propionate</td>
<td>Ointment, spray, foam, lotion, shampoo</td>
<td>Plaque and scalp psoriasis</td>
</tr>
<tr>
<td>Halobetasol propionate</td>
<td>Ointment</td>
<td>Plaque psoriasis</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>Cream, gel, lotion, foam</td>
<td>Plaque and scalp psoriasis</td>
</tr>
<tr>
<td>Mometasone</td>
<td>Cream, ointment, gel</td>
<td>Plaque and scalp psoriasis</td>
</tr>
<tr>
<td><strong>Vitamin D3 analogues</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcipotriol</td>
<td>Ointment, cream, solution</td>
<td>Plaque, scalp and nail psoriasis</td>
</tr>
<tr>
<td>Calcitriol</td>
<td>Ointment</td>
<td>Plaque psoriasis</td>
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<tr>
<td>Tacalcitol</td>
<td>Ointment</td>
<td>Plaque psoriasis</td>
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<tr>
<td><strong>Retinoids</strong></td>
<td></td>
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<tr>
<td>Tazarotene</td>
<td>Gel, cream</td>
<td>Plaque psoriasis</td>
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<tr>
<td><strong>Coal tar</strong></td>
<td>Ointment, gel, solution, shampoo, soap</td>
<td>Plaque and scalp psoriasis</td>
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<tr>
<td><strong>Anthralin</strong></td>
<td>Ointment, cream</td>
<td>Plaque psoriasis</td>
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<tr>
<td><strong>Calcineurin inhibitors</strong></td>
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<tr>
<td>(investigational use)</td>
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<tr>
<td>Tacrolimus</td>
<td>Ointment</td>
<td>Face, genitalia and intertriginous psoriasis</td>
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<td>Pimecrolimus</td>
<td>Cream</td>
<td>Intertriginous psoriasis</td>
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<td><strong>PDE4 inhibitors</strong></td>
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<tr>
<td>AN-2728</td>
<td>Ointment</td>
<td>Plaque psoriasis</td>
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**Combination Product**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Disease Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcipotriol + betamethasone dipropionate</td>
<td>Ointment</td>
<td>Plaque, scalp and nail psoriasis</td>
</tr>
<tr>
<td>Betamethasone dipropionate + salicylic acid</td>
<td>Ointment, cream, lotion</td>
<td>Plaque, scalp and nail psoriasis</td>
</tr>
</tbody>
</table>

Table 1. A summary of topical medications for psoriasis.
2. Guidances for effective management of psoriasis

Although there is no cure for psoriasis, several available therapies can help control skin lesions and associated symptoms. Some treatments can also induce remission for months or longer. Despite availability of numerous topical and systemic treatment options, there is a lack of patient satisfaction with the available treatments and high rates of non-compliance. In order to optimize topical treatment of psoriasis, guidelines have been developed for more effective management of psoriasis. Some of the available guidances for topical treatment are discussed in this section:

The American Academy of Dermatology (AAD) has published a six part series of guidelines in 2009, on the management of psoriasis and psoriatic arthritis. The third section of this series discusses the use of topical medications for the treatment of psoriasis (Menter et al., 2009). This guidance discusses the efficacy and safety of as well as offer recommendations for the use of topical corticosteroids such as vitamin D analogues, tazarotene, tacrolimus, pimecrolimus, emollients, salicylic acid, anthralin, coal tar, as well as combination therapy. The authors concluded that patients with localized psoriasis can be treated with topical agents, which generally provide a high efficacy-to-safety ratio. Topical agents may also be used adjunctively in patients with more extensive psoriasis who are undergoing therapy with either ultraviolet light, systemic or biologic medications. However, the use of topical agents as monotherapy in the generalized form of the disease or in the setting of limited, but recalcitrant, disease was not recommended.

The Cochrane Skin Group in UK published a review of topical therapies for chronic plaque psoriasis following examination of 131 studies (Mason et al., 2009). They concluded that vitamin D analogues showed similar efficacy as potent or very potent corticosteroids when used on the body, whereas topical corticosteroids proved the most effective treatment for scalp psoriasis. Combination of topical corticosteroids and vitamin D analogues were more effective than either agent as single formulation. Although the overall safety of topical therapies was high, topical corticosteroids were associated with lower incidence of local adverse events than vitamin D analogues. Warren et al. (Warren et al., 2010) has published a review summarizing the guidances on the use of topical, systemic and biological therapies for the treatment of psoriasis; co-morbidities associated with psoriasis; and complementary therapies for psoriasis. The UK National Health Service provides an annual evidence update on psoriasis and has included new guidelines and systematic reviews on psoriasis published or indexed from November 2008 to October 2009 in the 2009 Annual Evidence Update on Psoriasis from NHS Evidence – Skin Disorders.

In Germany, Nast et. al. have developed an evidence based guidelines for topical treatment (Nast et al., 2007). The guidelines focus on induction therapy in cases of mild, moderate, and severe plaque-type psoriasis in adults and contain a series of therapeutic recommendations. A similar guideline is also available for systemic treatment of psoriasis (Pathirana et al., 2009).

A guide has also been developed to optimize and harmonize the amount of topical medications to be applied on children (Long et al., 1998). Study conducted in children aged between 6 months to 9 years, showed that the amount of an ointment applied on children was similar to that predicted in accordance with these guidelines (Long et al., 1998).
3. Topical antipsoriatic medications

3.1 Corticosteroids

Topical corticosteroids, particularly high-potency corticosteroids, have been a mainstay in the topical treatment of psoriasis for decades (Bagel 2009). Their efficacy may be attributed to multiple mechanisms of action, including their anti-inflammatory, immunosuppressive and antiproliferative effects. Topical corticosteroids are often classified into seven classes in the United States and four in UK and Germany based on potency. A detailed classification system has been discussed elsewhere (Horn et al., 2010). In the United States, topical corticosteroids are classified as following: class I (superpotent), class II (potent), class III (upper mid strength), class IV (mid strength), class V (lower mid strength), class VI (mild) and class VII (least potent). Typically corticosteroids of lower potency are mainly used on the face and groin, and in infants and children. Mid-potency corticosteroids are typically used as initial therapy on all other areas in adults. Potent and superpotent corticosteroids are often used for stubborn, cutaneous plaques or lesions on the scalp, extremities, including palms, and/or soles as well as for initial therapy to achieve quick resolution of lesions. In this section detailed discussion of a few representative steroids are provided, however there are several other corticosteroids which are effective against psoriasis topically. Some steroids which are widely used in topical psoriasis treatment but have not been discussed in this section include, methylprednisolone aceponate (Ruzicka 2006), which has shown good efficacy against chronic therapy-resistant psoriasis, including both progressive and stationary phases. Although topical corticosteroids are effective in maintenance of the disease, these therapies can cause many potential local adverse effects including cutaneous atrophy, formation of telangiectasia, development of striae, steroid rosacea, perioral dermatitis, and skin infections (Horn et al., 2010). Risks of systemic adverse effects increase with prolonged use, or use of higher potency steroids, particularly with greater percent of BSA to which the topical steroid drug is applied. These risks include metabolic disturbances such as hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing like syndrome, osteonecrosis of the hip and immunosuppression are other rare but possible serious adverse events. Tachyphylaxis or tolerance often occurs with prolonged use, leading to less durable potency or lower effectiveness of topical steroids. Therefore, several strategies have been proposed to improve safety for long-term use of topical corticosteroids (Horn et al., 2010) such as, 1) using rotational treatment regimens that minimize side effects, 2) combination with other topical medications, 3) following package inserts on the maximum usage per week, and 4) caution when using in vulnerable body areas (such as face) and in children.

3.1.1 Clobetasol

Clobetasol propionate is a super high-potency glucocorticosteroid, initially approved for treatment of steroid-responsive dermatosis. Clobetasol propionate is traditionally formulated in an ointment base for treatment of psoriasis. However, several novel formulation of clobetasol propionate are now available such as spray, foam, lotion, and shampoo formulations, which may provide for improved convenience and acceptance in many patients with similar efficacy, safety, and tolerability as the traditional ointment and cream formulations (Feldman and Yentzer, 2009). While there are very few direct clinical comparison studies between clobetasol propionate in different vehicles, the efficacy rates of obtaining clear or almost clear of psoriasis are high for the novel formulations with most
patients achieving success after 2-4 weeks of treatment in well controlled clinical trials, but
the response rates are similar for all presentations. Small differences in vasoconstrictor
potency or cutaneous absorption have been noted among the formulations, but the clinical
significance of these observations is difficult to discern.

The development of a foam formulation of clobetasol propionate 0.05% (e.g. Olux®)
provides an effective and cosmetically appealing treatment option for patients with plaque-
type psoriasis because it spreads easily and is cosmetically elegant. Olux is based on
VersaFoam®, a thermolabile and low-residue foam. A randomised, placebo-controlled, double-blinded study of 279 patients aged 18 years or older with mild-to-
moderate plaque-type psoriasis demonstrated the efficacy and tolerability of clobetasol
propionate foam (Gottlieb et al., 2003). After 2 weeks of twice-daily applications of
clobetasol propionate foam versus vehicle foam, 68% of patients in the active treatment arm
were clear of lesions versus 21% of patients receiving placebo. The treatment was well
tolerated with 5% of patients receiving clobetasol propionate foam and 7% of those receiving
placebo reported burning at the site of application. Although the efficacy of the clobetasol
propionate foam can partially be attributed to patient adherence, the foam also delivers the
active drug more efficiently than other formulations that have been compared. This may be
due to the easier spread of foam onto the skin. In in vitro skin penetration studies,
application of foam to donor skin resulted in higher drug accumulation and increased rate
of permeation into skin layers (Huang et al., 2005).

A study comparing two novel formulations containing 0.05% clobetasol propionate, Clobex®
spray and Olux® foam clearly highlighted the difference in efficacy from two products
containing the same active ingredient (Mraz et al., 2008). In a study of 77 randomized
patients aged 18 years or older with moderate to severe plaque psoriasis the products were
applied as per the product labeling. At the end of the treatment period (2 weeks for foam
and 4 weeks for spray), patients treated with clobetasol propionate spray showed a
significantly greater median reduction in affected body surface area compared to the
clobetasol propionate foam. Improvements in quality of life were statistically significantly
greater at all time points for patients treated with clobetasol propionate spray compared to
patients treated with the foam formulation. The majority of adverse events for both products
were mild in severity (Mraz et al., 2008).

Clobex® shampoo containing 0.05% clobetasol propionate is a once-daily, short-contact,
shampoo treatment for moderate-to-severe scalp psoriasis (Feldman & Yentzer, 2009). The
efficacy and safety of clobetasol propionate 0.05% shampoo was evaluated in a randomized,
double-blind, vehicle-controlled clinical trial of 142 patients aged 12 years and older with
moderate-to-severe scalp psoriasis (Jarratt et al., 2004). Patients applied clobetasol
propionate shampoo or vehicle shampoo once daily for 15 minutes for four weeks.
Treatment success (defined as a global psoriasis rating of "clear" or "minimal") was obtained
for 42% of patients who used clobetasol propionate shampoo versus 2% of patients who
used vehicle shampoo. Recurrence of the scalp psoriasis, assessed during a two week
follow-up period, showed that the clobetasol propionate shampoo was more effective than
the vehicle shampoo in preventing recurrence after treatment was discontinued. Similar
safety profile was established between the clobetasol propionate shampoo and vehicle
shampoo. No skin atrophy, telangiectasia, acne or severe adverse events were noted for
either treatment group (Jarratt et al., 2004).
3.1.2 Mometasone

Mometasone furoate (Elocon® cream) is a potent synthetic glucocorticoid, which is commonly used in dermatological conditions (Prakash & Benfield 1998). It is available as cream, ointment and lotion formulations for the treatment of patients with atopic dermatitis, seborrhoeic dermatitis, scalp psoriasis and psoriasis vulgaris. Although mometasone demonstrates greater anti-inflammatory activity and a longer duration of action than betamethasone, it has low potential to cause adverse systemic effects such as suppression of the hypothalamic-pituitary-adrenal (HPA) axis. Moreover, its atrophogenic potential is low and no greater than that of other glucocorticoids in its class, such as betamethasone valerate. Transient, mild to moderate, local adverse effects such as burning, stinging, folliculitis, dryness, acneform eruptions and signs of skin atrophy have been reported with mometasone. Mometasone has shown a low risk of primary sensitization and cross-reactions in preliminary patch test studies.

In clinical studies with patients aged between 12 and 90 years, with moderate to severe scalp psoriasis (Swinehart et al., 1989; Vanderploeg et al., 1989) or psoriasis vulgaris (Bressinck et al., 1988; Svensson et al., 1992), who had not used topical glucocorticoids for 2 weeks or taken systemic glucocorticoids for 6 weeks prior to enrolment showed that in general, mometasone (0.1% lotion, ointment or cream applied once or twice daily) was significantly superior to topical glucocorticoid preparations of similar and weaker potency. The ointment formulation of mometasone was significantly superior to once-daily hydrocortisone 1.0% ointment (Bressinck et al., 1988; Katz et al., 1989), twice-daily betamethasone valerate 0.1% ointment (Svensson et al., 1992; Medansky et al., 1987), triamcinolone acetonide 0.1% ointment (Medansky et al., 1988), and 3 times daily fluocinolone acetonide 0.025% ointment (Medansky et al., 1988).

The effectiveness of alternate-day treatment with mometasone 0.1% ointment in maintenance therapy of psoriasis vulgaris was evaluated in a randomized, double-blind, 3-week study in 48 adult patients with moderate psoriasis vulgaris. After 1 week (n = 48) of once-daily application of mometasone 0.1% ointment, patients either continued with daily application (n = 25) or applied mometasone 0.1% ointment on alternate days (n = 19) for 2 weeks. At the end of the study period both regimens were effective in treating disease signs and symptoms with no detectable difference between the treatment groups (Prakash & Benfield 1998).

In patients with scalp psoriasis, the effects of mometasone lotion were significantly superior to those of twice-daily application of betamethasone valerate 0.1% lotion or triamcinolone acetonide 0.1% lotion (Swinehart et al., 1989; Vanderploeg et al., 1989).

A study in 24 patients with moderate to severe psoriasis evaluated the response to mometasone 0.1% ointment applied once daily on the face and intertriginous areas and other affected body areas (Lebwohl et al., 1993) After 2 weeks, the face and intertriginous areas showed a quicker and significantly superior response to treatment as compared with other body areas (Lebwohl et al., 1993).

3.1.3 Betamethasone

Betamethasone dipropionate (BDP, Diprolene®) is a mid-potency synthetic fluorinated corticosteroid and is commonly used in combination with vitamin D3 analogues (Saraceno
et al., 2009). Betamethasone dipropionate is commonly formulated as a gel. Several attempts have been made to increased betamethasone dipropionate skin permeation by encapsulating in liposomes. The liposomal formulations achieved improved corticosteroid dermal delivery (Fresta & Puglisi 1997). However, in a double blind randomized trial comparing a liposomal formulation containing 0.039% betamethasone dipropionate against the gel containing 0.064% betamethasone dipropionate, showed that the gel was more effective in reducing psoriatic plaques than the liposome after application for 14 days (Korting et al., 1990). Hence, liposome encapsulation of betamethasone dipropionate may increase the anti-inflammatory action but not the antiproliferative effect.

Betamethasone valerate (BMV) is also available as a foam formulation (Luxiq®) containing 0.12% betamethasone valerate for use as a treatment for psoriasis affecting the scalp (Feldman et al., 2001) and non-scalp (Stein et al., 2001) regions of the body. Betamethasone valerate foam formulated in a thermolabile hydroethanolic foam vehicle is absorbed more rapidly, and demonstrated 2-fold greater skin penetration in a human cadaver skin model, than the betamethasone valerate lotion (Franz et al., 1999). Safety and efficacy of the betamethasone valerate foam was evaluated in a randomized, multicenter, double-blind, active- and placebo-controlled trial in adult patients with moderate to severe scalp psoriasis (Franz et al., 1999). At the end of 28-days of treatment, patients on betamethasone valerate foam showed significantly better clearing of plaques than those on betamethasone valerate lotion and placebo. Further, there was no evidence of increased toxicity for betamethasone valerate foam (Franz et al., 1999).

3.1.4 Halobetasol

Halobetasol propionate (HP) is a high potency corticosteroid available as 0.05% ointment and cream (Rivera & Hsu 2005). Halobetasol is a synthetic trihalogenated corticosteroid structurally similar to clobetasol propionate but with an additional fluorine atom (Rivera & Hsu 2005).

The efficacy and safety of 0.05% halobetasol ointment (Ultravate®) in the treatment of patients aged 18 years or older with moderate plaque psoriasis was demonstrated in two multicenter, randomized, double-blind, and placebo controlled studies in 204 patients (Bernhard et al., 1991). In both studies the medication and placebo were applied twice daily for 2 weeks. At the end of the treatment period, 0.05% halobetasol ointment was found to be more effective over placebo. No systemic adverse events or findings of skin atrophy were reported in these studies. Reports of “stings” or “burns” were equally divided between halobetasol formulation and its vehicle. These two studies demonstrated that 0.05% halobetasol ointment was clinically beneficial and without evidence of significant adverse events during the treatment period.

Three clinical studies separately compared the 0.05% halobetasol propionate ointment to 0.05% clobetasol propionate ointment (Goldberg et al., 1991), 0.05% betamethasone dipropionate (BDP) ointment (Mensing et al., 1991) and 0.1% betamethasone valerate (BMV) ointment (Blum & Yawalkar 1991) in plaque psoriasis. The efficacy of the halobetasol propionate ointment was significantly superior to those of the other products in these studies. Neither skin atrophy nor systemic adverse effects were observed for halobetasol propionate during 4 weeks. However, because of the risks associated with prolonged use reported in upto

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13% of patients, the daily application of halobetasol propionate should be limited to a maximum of 14 days with a maximum dose of 50 g per 2 weeks (Rivera & Hsu 2005).

3.2 Vitamin D3 analogues

The active form of vitamin D3 is known to play an important role in the regulation of intestinal calcium absorption, bone mineralization and the prevention of rickets. In addition to these actions, vitamin D3 has several additional biological effects including the stimulation of cellular differentiation, inhibition of proliferation and immunomodulation (Muller & Bendtzen, 1996). This makes vitamin D3 a potential candidate for treatment of psoriasis. However, parent vitamin D3 might not be suitable for treating psoriasis due to potential for hypercalcemia. Hence, several vitamin D3 analogues have been developed for treatment of psoriasis (Tanghetti 2009). Vitamin D analogues bind to the vitamin D receptor, thus causing biological actions on both cornocytes and on immune-competent cells in the skin. Analogues such as calcipotriol, calcitriol, tacalcitol and maxacalcitol inhibit cornocyte proliferation and stimulate cornocyte differentiation in vitro. In addition, these analogues have only minimal effects on calcium levels and calcium excretion (Barker et al., 1999). However, due to concerns with elevating the serum calcium levels with extensive application to large body surface area, these analogues usually have a limit on total amount used per week.

3.2.1 Calcipotriol (Calcipotriene)

Calcipotriol is a synthetic vitamin D3 analogue formulated as a cream and scalp solution (Dovonex®) at a drug loading of 0.005%. The calcipotriol cream is effective in treatment of plaque psoriasis and statistically significantly better than the placebo alone (Staberg et al., 1989). In addition, a solution has been developed for scalp psoriasis (Klaberg et al., 1994), and calcipotriol ointment has also been investigated for nail psoriasis (Tosti et al., 1998).

A comparison of calcipotriol ointment with a combination of betamethasone dipropionate and salicylic acid ointment (Diprosalic®) showed that calcipotriol was as effective as the combination product for treating nail psoriasis (Tosti et al., 1998). Comparisons of 0.005% calcipotriol ointment and 5% coal tar ointment in conjunction with sun exposure in 10 adult patients with stable plaque psoriasis showed that both calcipotriol and coal tar ointment had comparable efficacies in treating stable plaque psoriasis when used simultaneously with sun exposure, although the initial response to calcipotriol was faster (Kaur et al., 2001).

The calcipotriol cream formulation is less greasy than the ointment formulation and hence has better patient acceptability. It was the impression that the effect of calcipotriol is more pronounced on lesional infiltration and scaling, whereas the effect is less pronounced on the vascular component of psoriasis, as determined by redness. Finally, the therapeutic response to calcipotriol ointment can be increased by occlusion with a polyethylene film (Boyrke et al., 1993).

3.2.2 Calcitriol

Calcitriol is a synthetic form of the active metabolite of vitamin D3. It has anti-proliferative, prodifferentiating and immunomodulating effects on human keratinocytes (Lehmann 2009).
A calcitriol ointment (Vectical®) for mild-to-moderate plaque psoriasis was approved by the US Food and Drug Administration (FDA) in 2009 (Kowalzick 2009). Multicenter and randomized clinical trials have shown calcitriol ointment to be efficacious, safe and cosmetically acceptable as compared to placebo and other topical psoriasis therapies (Kircik 2009). Pharmacokinetic studies in patients with psoriasis and healthy control subjects have demonstrated that topical calcitriol ointment produced minimal systemic absorption of calcitriol and does not alter systemic calcium homeostasis significantly even when applied to approximately one third of the body surface area (Kircik 2009). However, the Vectical® prescribing information limits the use to 200 gm per week due to concern of disturbance in calcium metabolism. The efficacy and safety of topical calcitriol ointment were examined in two placebo-controlled, randomized, multicenter, parallel-group double blind clinical trials of identical design in a total of 839 patients aged 18 years or older with mild-to-moderate plaque psoriasis (Lebwohl et al., 2007). Both studies showed that at the end of the treatment period, the patients in the calcitriol group showed significantly better clearing of psoriatic plaques than those in the vehicle group. The incidence of treatment related adverse events such as mild skin discomfort, pruritus, and erythema was similar for the calcitriol and the vehicle groups in both studies (Lebwohl et al., 2007).

3.3 Retinoids

Retinoids provide a distinct class of treatment option within antipsoriatic therapies, which are largely dominated by immunomodulatory effects. The mechanism of action of retinoids in psoriasis may include direct suppression of inflammation as well as inhibition of proliferation and normalization of differentiation in the epidermal layer (van de Kerkhof 2006). In the US topical retinoid for psoriasis is approved as tazarotene gel and cream (Tazorac®) available in 0.05% and 0.1% formulations. It is recommended that treatment commences with the 0.05% formulation, and the concentration increased if necessary and tolerated. Tazarotene is applied once daily in the evening. All formulations and strengths can be used for plaque psoriasis. In general, gels and the more-concentrated strengths tend to have higher incidences of irritation, pruritus, erythema, stinging and desquamation (Yamauchi et al., 2004). The cream formulations are being marketed as less irritating (Linden & Weinstein 1999). A recent improvement in tazarotene therapy was a reduction of skin irritation by short contact applications or concurrent steroid use (Veraldi & Schianchi 2003). These side effects are most apparent on initial application, but are generally alleviated with continued usage. Tazarotene is contraindicated in pregnant women and in women who are not taking adequate birth control in view of its teratogenic potential, category X pregnancy status. In addition, tazarotene use should be avoided in nursing women, and patients who have substantial sun exposure, who do not use adequate sun protection and who use photosensitizers or have photodermatitis (Veraldi & Schianchi 2003).

The efficacy of once-daily topical tazarotene has been studied in four randomized, double or single blinded clinical trials; two trials on the tazarotene gel formulation (Lebwohl et al., 1998; Weinstein et al., 1997) and two trials on tazarotene cream formulation (Weinstein et al., 2003) in patients at least 18 years old and having plaque psoriasis in at least 2% of the total body surface area. The duration of active treatment was 12 weeks and an additional 12 weeks follow-up period without active treatment was incorporated in these studies. These studies showed that as early as at week 1, tazarotene 0.1% formulation showed a statistically
significant improvement as compared to the vehicle, with the 0.05% tazarotene formulations showing statistically significant improvement at week 4. Twelve weeks after the discontinuation of therapy (post-treatment phase), both 0.1% and 0.05% tazarotene cream were significantly better as compared to the vehicle (Weinstein et al., 2003). Comparative studies between calcipotriol and tazarotene monotherapy have been carried out, showing superior efficacy of calcipotriol during the first 8 weeks but equal efficacy after 12 weeks' treatment (Tzung et al., 2005). The penetration of tazarotene through human skin is limited. The systemic availability after topical tazarotene 0.05% or 0.1% gel is <1% after single application, and 2.6% and 5.3%, respectively, after once-daily applications following 2 weeks of treatment. After 12 weeks of treatment, the systemic availability of tazarotene 0.05% was 1.8% and for the 0.1% tazarotene preparation it was 3.9% (Tang-Liu et al., 1999).

3.4 Other topical agents

While tars, anthralsins and salicylic acid containing products have been used for decades in the United States for the treatment of plaque psoriasis, recent innovative delivery technologies have provided new versions of these products, offering the prospect of enhanced tolerability, convenience and compliance. Some of these novel topical products are discussed in this section.

3.4.1 Anthralsins

A timed-release cream of anthralin (Psoriatec®) has been developed with the potential to reduce skin irritations that are sometimes observed with generic anthralin. Psoriatec can be a relatively convenient formulation to reduce side effects, such as irritation and skin staining, by following instructions for short contact anthralin therapy (SCAT).

3.4.2 Coal tar

An emollient foam formulation of coal tar (Scytera™) has been developed for convenient usage to relief of the symptoms of psoriasis. This formulation is neither intended for use for prolonged periods nor in areas such as rectum, genital area, or eyes. As with other tar containing products, skin exposure to sunlight should be avoided after application and it has the potential to stain clothing, contact lenses, and hair. Some tar products are also available as co-packaged kits, one such example is Clobeta Plus®. This product is co-packaging of clobetasol cream and coal tar solution.

3.4.3 Salicylic acid

Salicylic acid as a topical agent aids in the removal of excessive keratin in hyperkeratotic skin disorders, including psoriasis (including body, scalp, palms and soles) (Beani 2002). Salicylic acid has been shown to produce desquamation of the horny layer of skin while not affecting qualitative or quantitative changes in the structure of the viable epidermis. It has been used as monotherapy or as combination therapy to reduce the size and scale of psoriatic plaques. Recent development of foam formulations of salicylic acid such as Salvax® and Salkera® may lead to broader use of this agent. In children under 12 years of age and those patients with renal or hepatic impairment, the area to be treated should be limited and
the patient monitored closely for signs of salicylate toxicity. Contact with eyes and other mucous membranes should be avoided.


4.1 Calcineurin Inhibitors

These agents inhibit the activity of calcineurin phosphatase, an enzyme important for the translocation of the pluripotent transcription factor, nuclear factor of activated T cell, from the cytoplasm to the nucleus where it activates a number of proinflammatory cytokines associated with T-cell activation. Hence, these agents have potential for treatment of skin diseases mediated by calcineurin phosphatase (Luger & Paul 2007). Currently these calcineurin inhibitors are approved for use in mild to moderate atopic dermatitis only, any use in psoriasis is off-label, and therefore not within approved US-FDA prescribing information. A black box warning has been added to the labels of these medications stating that the long-term safety of topical calcineurin inhibitors has not been established and that rare cases of cancer have been reported in patients who used the medications, although a causal relationship in human beings has not been established. Apart from topical tacrolimus and pimecrolimus, another new oral calcineurin inhibitor, voclosporin is also in clinical development for treatment of plaque psoriasis (Papp & Carey 2010).

4.1.1 Tacrolimus

Tacrolimus is an immunosuppressive drug whose main use is after allogenic organ transplant to reduce the activity of the patient’s immune system and hence reduce the risk of organ rejection. It is also used in a topical ointment preparation (Protopic™) for the treatment of severe atopic dermatitis, vitiligo and psoriasis. Tacrolimus ointment was approved in the United States in 2000, and Europe in 2001 for atopic dermatitis. However, new research has proven the potential use of tacrolimus in psoriasis (Luger & Paul 2007; Beck 2005). The introduction of tacrolimus ointment marked the advent of a new, nonsteroidal drug class, topical immunomodulators, for the management of inflammatory dermatoses.

Tacrolimus ointment seems most effective in treating psoriasis where the skin is thin, that is on the face, genitelia and intertriginous areas (Martín Ezquerra et al. 2006). In one study 21 patients with facial psoriasis lesions applied tacrolimus (0.1%) ointment twice a day for 4 weeks without occlusion. A complete or good response was obtained in majority of the patients (Yamamoto & Nishioka 2003).

The efficacy and tolerability of tacrolimus ointment has also been investigated for the treatment of male genital psoriasis (Bissonnette et al., 2008). In an open-label study in 12 adult male patients with genital psoriasis, patients received topical tacrolimus 0.1% ointment twice daily for 8 weeks followed by a 4-week observational period. Psoriasis severity also improved significantly for the glans, shaft of the penis, and scrotum. The ointment was very well tolerated, with only mild pruritus or burning sensation of limited duration reported (Bissonnette et al., 2008).

The safety and efficacy of tacrolimus (0.1 %) ointment for the treatment of psoriasis on the face, intertriginous areas, or both were evaluated in an open-label, clinical trial of 21 patients with psoriasis (Freeman et al., 2003). A total of 81 percent of patients experienced complete
clearance at day 57 (end of treatment). Only 2 patients reported adverse events, which were limited to itching and the feeling of warmth at the application site (Freeman et al., 2003).

4.1.2 Pimecrolimus

Pimecrolimus is a non-steroidal immunosuppressant derived from ascomycin. Pimecrolimus 1% cream (Elidel\textsuperscript{®}) was approved in the United States, the European Union, and Japan as second-line therapy for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in patients, who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable (Fabroni & Wollina, 2009). Pimecrolimus also has an enormous potential as topical treatment for numerous inflammatory skin diseases like psoriasis and dermatitis (Fabroni & Wollina, 2009).

Pimecrolimus is not effective in plaque-type psoriasis when used as the commercially available formulation without occlusion (Wollina et al., 2006). However, pimecrolimus has been shown to be effective in intertriginous psoriasis (Wollina et al., 2006). A double-blind, randomised, vehicle-controlled study was performed in 57 patients aged 18 years or older with moderate-to-severe intertriginous psoriasis. By week 8 of treatment, 82% of patients using pimecrolimus scored their disease as being equally well, or completely controlled, compared with 41% of the vehicle group. The pimecrolimus treatment was also well tolerated (Gribetz et al., 2004).

4.2 Phosphodiesterase 4 (PDE4) Inhibitors

PDE4 is the predominant cyclic AMP degrading enzyme, present in a variety of inflammatory cells including eosinophils, neutrophils, macrophages, T cells and monocytes. In addition, this enzyme is expressed in non-immune cells such as keratinocytes and fibroblasts. Due to the broad anti-inflammatory and immuno-modulatory action of PDE4 inhibitors, it has been proposed that PDE4 inhibitors might also be efficacious for skin disorders such as psoriasis and atopic dermatitis (Bäumer et al., 2007). These PDE4 inhibitors displayed strong anti-inflammatory action in models of allergic contact dermatitis in mice, in the arachidonic acid induced skin inflammation in mice and in ovalbumin sensitized guinea pigs. The determination of cytokines in skin homogenates revealed that both Th1 as well as Th2 cytokines are suppressed by PDE4 inhibitors, indicating an anti-inflammatory activity in both the Th2 dominated acute phase as well as the Th1 dominated chronic phase of atopic dermatitis. Due to the suppression of Th1 cytokines, activity can also be expected in psoriasis (Bäumer et al., 2007). Consequently PDE4 inhibitors are currently in clinical development for treatment of psoriasis both topically (AN-2728 from Anacor Pharmaceuticals) and orally (CC-10004 from Celgene Corporation).

4.2.1 AN-2728

A recent publication gives a comprehensive summary of preclinical, phase I and phase II data for topical AN-2728 (Nazarian & Weinberg, 2009). Till date 3 phase IB, 1 Phase IIA and 1 phase IIB trials have been completed for AN-2728, and results suggest that AN-2728 is well tolerated with significantly better efficacy in plaque psoriasis as compared to placebo controls. A phase IIB, randomized, double-blind, placebo-controlled, parallel-assignment, single-center, safety and efficacy clinical trial assessed AN-2728 ointment (5% bid for 12
weeks) in 30 patients with plaque psoriasis (Nazarian & Weinberg 2009). Preliminary data revealed that psoriatic plaques treated with AN-2728 exhibited a reduced overall target plaque severity score compared with plaques treated with vehicle alone at 8 weeks of treatment. In addition, AN-2728 topical therapy has also been reported to be well tolerated. In the phase IIA trial, no treatment-related adverse events or laboratory anomalies were reported; one patient reported mild gingivitis and diarrhea, but these effects were not considered to be related to the trial medication (Nazarian & Weinberg 2009).

4.3 Janus-Associated Kinase (JAK) inhibitors

The JAK family is composed of four tyrosine kinases - JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2) (Fridman et al., 2011). Members of the JAK family are essential for signaling by many cytokines and growth factors following their binding to specific receptors on the cell surface. The interaction activates one or more JAKs, JAKs in turn activate the signal transducer and activator of transcription (STAT) proteins that transmit the growth and activation signals to the nucleus. JAK signaling is involved in a number of biologic processes, including the formation and development of blood cells and the regulation of immune function. Hyperactivation of JAKs has been associated with a number of disease states, including chronic myeloproliferative disorders and inflammatory diseases such as rheumatoid arthritis (RA) and psoriasis (Fridman et al., 2001). As a result, JAK inhibitors are currently in clinical development for treatment of psoriasis both topically (INCB18424 from Incyte Corporation) and orally (Tofacitinib from Pfizer).

A 28-day phase Ib/IIa dose escalation trial of topical INCB18424 in patients with mild-to-moderate psoriasis demonstrated rapid onset of action, reduction in total lesion area, and improvement in lesion thickness, erythema, and scaling (Mesa 2010).

5. Combination topical therapies

The commonly used topical medications described in this chapter provide efficacy through varying and divergent pathways. As these agents act through different mechanisms, there is a scientific rationale for their use in combination therapy. The rationale assumes that agents are selected on the basis of their individual mechanisms of action, which may offer the possibility of additive or synergistic efficacy, reduction in the dose of either or both products, and reduction in the occurrence of side effects (Norris 2005). Several studies have proven the advantages of using a combination of topical medications for treatment of psoriasis. Recently, a fixed dose combination ointment containing 50 μg/g calcipotriol and 0.5 mg/g betamethasone dipropionate (approved in US as Taclonex®) was found to be effective against psoriasis vulgaris (Claréus et al., 2009). This ointment formulation combines the keratinocyte differentiation and antiproliferative action of the vitamin D₃ analogues (calcipotriol) with the anti-inflammatory effect of steroids (betamethasone dipropionate), thus enhancing effectiveness while reducing the side-effect profile of the individual agents (Saraceno et al., 2009). It was found that the combination product had a more rapid onset of action (Papp et al., 2003) than calcipotriol or betamethasone alone and was more effective (Douglas et al., 2002) than calcipotriol or betamethasone alone. In a clinical trial with 1605 randomized patients aged 18 years or older showed that the combination product (Taclonex®) was significantly more effective than betamethasone,
calcipotriol and placebo. The local adverse reactions were also low compared to the other drugs. It was concluded that two different treatment regimens (i.e. application once or twice daily) employing the two-compound product provided rapid and marked clinical efficacy as compared to calcipotriol or betamethasone alone and also were safe therapies for psoriasis vulgaris (Saraceno et al., 2009). Combination of calcipotriol and betamethasone has also been shown to have significant advantages in treatment of scalp and nail psoriasis (Saraceno et al., 2009). More recently, a combination of 0.005% calcipotriol and 0.064% betamethasone dipropionate (Taclonex Scalp® in US and Xamiol® in Europe) has been approved for the treatment of moderate to severe scalp psoriasis vulgaris in adults. This once-daily therapy has a quick onset of action and greater efficacy than monotherapy with either ingredient. At 8 weeks, the combination product had a safety profile comparable with betamethasone dipropionate and was associated with significantly fewer adverse events than calcipotriol (Guenther 2009).

A combination of betamethasone dipropionate and salicylic acid (Diprosalic®) is available as ointment and lotion formulations. Faster improvement in scaling, itching, and redness has been observed with Diprosalic® as compared to betamethasone dipropionate alone (Guenther 2004). It has also been shown that the combination ointment has similar efficacy to clobetasol and calcipotriene (calcipotriol) ointments.

A multicentre, randomised, double-blind, vehicle-controlled, parallel-group study was carried out to study the effect of the addition of calcipotriol ointment to methotrexate in patients aged 18 years or older with psoriasis vulgaris (De Jong 2003). From this study, it was concluded that the combined use of calcipotriol with methotrexate resulted in a methotrexate-sparing effect, while still maintaining the efficacy. Calcipotriol treatment increased the time to relapse of psoriasis following discontinuation of methotrexate. The combination of calcipotriol and methotrexate was safe and well tolerated. The combination resulted in lower cumulative doses of methotrexate as compared to monotherapy, thus significantly reducing the risk of methotrexate side effects (De Jong 2003).

The combination of calcipotriol ointment (twice daily) and tazarotene gel (once daily) was compared with clobetasol ointment (twice daily) in the treatment of psoriasis (Bowman et al., 2002). The vitamin D3 analogue plus retinoid treatment had comparable efficacy to that of the potent topical steroid. Similarly a comparison of twice-daily calcipotriol ointment against the combination of tazarotene gel and 0.1% mometasone furoate cream was superior during the first 2 weeks of treatment. However, by 8 weeks of treatment, both groups exhibited similar responses (van de Kerkhof 2006).

6. Combination of topical therapy with phototherapy

Phototherapy for psoriasis includes narrowband and broadband UVB phototherapy; psoralens combined with UVA, targeted excimer laser phototherapy, and combination treatments (Nguyen et al., 2009). The combination of phototherapy with topical products has long been used for treatment of plaque psoriasis. In the 1920s, William Goeckerman combined the use of UVB phototherapy with topical application of tars (Su & Fang 2008; Witman 2001). This in-patient psoriasis regimen, known as the Goeckerman regimen, is still occasionally used in major dermatologic centers.
Psoralen photochemotherapy uses a combination of topical application (or ingestion) of 8-methoxypsoralen followed by exposure of the affected skin area to long-wavelength UV (320 - 400 nm) (Nguyen et al., 2009). Other psoralen derivatives such as 5-methoxypsoralen and 4,5,8-trimethylpsoralen are also used in topical PUVA therapy. Bath psoralen UVA combination involves immersion of either localised areas (such as the hands or feet) or the whole body in water containing dissolved 8-methoxypsoralen prior to UVA exposure (Nguyen et al., 2009).

Photodynamic therapy is another non-invasive technique used in the treatment of skin diseases. 5-aminolevulinic acid is a prodrug that is metabolized intracellularly to form the photosensitizing molecule protoporphyrin IX. When protoporphyrin IX is activated by light, cytotoxic reactive oxygen species and free radicals are generated. This phototoxic effect may be used for treatment of malignant and non-malignant hyperproliferative tissue (Gupta & Ryder 2003). Photodynamic therapies using 5-aminolaevulinic acid in plaque psoriasis has also been reported (Gupta & Ryder 2003), however these are not approved regimens. Side effects of the aforementioned regimens include short and long term adverse effects of visible and UV light, such as acute phototoxicity, and longer term effects such as photoaging and photocarcinogenesis. Protective clothing, sunblock and sunglasses should be used to protect unaffected areas of the body.

7. Sequential therapy

Sequential therapy is a strategy to treat psoriasis using a specific combination of therapeutic agents in a particular sequence with the aim of achieving initial efficacy followed by a safe maintenance regimen (Koo 1999). This treatment strategy maximizes efficacy of each medication while minimizing long term side effects. The strategy involves three main steps – 1) clearing phase, 2) transitional phase and 3) maintenance phase (Koo 1999). A combination of topical, systemic and phototherapy agents can be used to achieve the desired outcome, depending on the severity of the disease (Lebwohl et. al., 2004).

The clearing phase involves the use of a rapid acting agent such as a potent or super-potent topical steroid at the maximum dermatologic dose with the main aim of promptly controlling an acute outbreak of psoriasis. This is followed by the transitional phase, in which a well tolerated maintenance agent such as acitretin or vitamin D analogue is introduced and administered along with the clearing agent. The clearing agent is slowly tapered off in this phase of treatment. The transitional phase can be challenging as it requires prevention of breakthrough of the disease, while tapering off the clearing agent and adjusting dose of the maintenance agent to ensure long term control with minimal side effects. Finally, in the third phase of the treatment, the patient is retained on the maintenance therapy, with additional therapy such as phototherapy, as needed (Koo 1999).

Several combinations of therapeutic agents and regimen for sequential therapy have been proposed in literature (Lebwohl et. al., 2004; Bhutani et. al., 2011). However the choice of treatment agents needs careful consideration based on the severity and type of the disease, and the need to balance safety and efficacy. Recently, a sequential treatment regimen of clobetasol and calcitriol has been shown to be efficacious and safe for the management of moderate-to-severe plaque psoriasis (Brodell et. at., 2011). In a multicentre, open-label study in subjects aged 18-80 years with moderate-to-severe plaque psoriasis, the patients applied
clobetasol propionate (0.05% spray) twice daily for up to four weeks. At the end of four
weeks, if the patient's overall disease severity was assessed as clear, almost clear, mild or
moderate, the patients were treated with calcitriol (3 μg/g ointment) twice daily for an
additional eight weeks (upto week 12) or unless the patient's disease was assessed as severe
or returned to the baseline score, at which time the treatment was discontinued. Patients
were evaluated at baseline and at 2, 4, 8 and 12 weeks. In 84% of the patients who completed
the 12 week study, this treatment resulted in at least one grade improvement in disease
severity and hence was considered successful as per predefined criteria. There was a
significant decrease in the percent body surface area affected, from 7.1% at baseline to 3.9%
at week 12. The sequential treatment regimen was also well tolerated with no unexpected
adverse events. Most reported adverse events and skin irritations were mild in severity
(Brodell et. at., 2011).

8. Challenges in developing topical medications for psoriasis

The unique nature of drug delivery across the skin also presents with several unique
challenges in development of topical products, such as:

1. Optimization of both drug property and formulation composition to enhance the rate
   and extent of drug diffusion through the stratum corneum;
2. Reduced drug concentration and increase in data variability due to presystemic
   metabolism in the skin;
3. Switch of topical formulations during clinical development that can be very
   challenging, hence only minimal formulation changes can be usually made during
   development;
4. No control on deep tissue penetration through formulation approaches, which is
   primarily influenced by protein binding and dermal blood flow;
5. Lack of confidence in dose projection due to difficulty in establishing robust skin
   pharmacokinetic-pharmacodynamic relationship;
6. High variability in \textit{in vitro} and \textit{in vivo} skin permeability remains a major obstacle in
   using these tools in formulation development;
7. Guidances from regulatory agencies often call for clinical comparisons of innovative
   drugs with approved active comparators, thus increasing the challenges for
   development and licensure of novel products;
8. Regulatory standards call for demonstration of benefit for each component within a
   fixed dose combination product, the so-called "Combination Rule", another challenge in
   development of a combination product.

In addition to these general challenges in topical formulation development, there are
several challenges specific to psoriasis and the development of antipsoriatic topical
products, such as:

1. Psoriatic lesions can have both thickened and markedly thinned epidermis, this
   heterogeneity in the skin morphology can increase the variability in drug permeation
   and systemic absorption, thus increasing challenges in formulation development;
2. A significant number of psoriasis patients feel that the current therapies are either not
   sufficiently efficacious or aggressive. Hence, a primary challenge is to develop new
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therapies which can be once daily application and show quick response, such as within the first four weeks of treatment;

3. Effective management of psoriasis frequently necessitates combining therapies in order to achieve optimum response while minimizing any side-effects. Thus any new topical therapy should have appropriate safety and efficacy when used in combination with another topical medication, systemic therapy and/or phototherapy;

4. In order to increase patient adherence to therapy, new topical formulations should have appropriate cosmetic elegance such as ease of use, no or minimal staining potential on clothing and bedding, quick absorption on application and being less greasy;

5. Formulations which can be used on many areas of the body including hair-bearing sites are preferred as patients often have psoriasis plaques in multiple areas;

6. Due to the availability of a wide variety of therapies and presence of generic products in the market, competitive cost of any new medication is paramount in influencing physician's and patient's choice of product.

9. Conclusion
As is summarized in this chapter, there are several treatment options for psoriasis and exciting novel targets (e.g. PDE4 and JAK) are being investigated as potential topical treatment options. Also, combination topical products and combination of topical and phototherapy have been shown to provide more effective treatment options. The epidermal hyperproliferation in psoriatic patients may increase the variability in drug penetration across the skin. Hence novel drug delivery approaches such as liposomes, iontophoresis, and electroporation are being investigated for improved delivery. Recent research has emphasized the importance of treatment adherence in the management of psoriasis. Adherence to treatment is likely to be a far more important determinant of success than are small differences in drug delivery, especially in actual clinical use as opposed to the well controlled environment of clinical trials. Several guidances have been developed to optimize topical treatment of psoriasis and hence enable more effective management of psoriasis. Since patients prefer a less messy vehicle, adherence and outcomes are likely to be better with the more novel formulation options such as foams and sprays compared with the traditionally recommended ointment.

10. Declaration of interest
The authors are employees of Merck Research Laboratories, a division of Merck Sharp and Dohme Corporation, which markets certain topical therapies discussed in the chapter.

11. References
Psoriasis


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We hope you enjoy and find the information provided in this book useful in your research or practice. We urge that you continue to keep abreast of the new developments in psoriasis and share your knowledge so that we may advance treatment and cures of psoriasis.

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