Therapeutic Class Overview
Topical Psoriasis Agents

Therapeutic Class

- **Overview/Summary:** The focus of this review will be the topical agents used for the treatment of psoriasis.[1-9] These agents include the vitamin D analogs calcipotriene and calcitriol along with the retinoid tazarotene. Calcipotriene is also formulated with betamethasone in a combination product. Each of these medications are Food and Drug Administration (FDA) approved for the treatment of plaque psoriasis. Certain calcipotriene products also have the indication for treatment of scalp psoriasis. In addition to psoriasis, tazarotene is approved for the treatment of acne vulgaris, however its use for this indication will not be included in this review.[1-9] The exact mechanisms of action of the vitamin D analogs and topical retinoids is unknown. The vitamin D analogs are believed to involve the drug's ability to inhibit keratinocyte proliferation and stimulate keratinocyte differentiation.[10] The activated tazarotene binds to all three members of the retinoic acid receptor (RAR) family: RARα, RARβ, and RARγ, but shows relative selectivity for RARβ, and RARγ and may modify gene expression. The clinical significance of this is unknown.[8,9]

  Psoriasis is a common chronic skin disorder typically characterized by erythematous papules and plaques with a silver scale, although other presentations occur. Most cases are not severe enough to affect general health and are treated in the outpatient setting.[10] The options for treatment are topical or systemic and depend on the severity of the disease. Mild-to-moderate disease can often be managed with topical agents, while patients with moderate-to-severe disease may need systemic therapy. Moderate-to-severe disease is usually considered to effect more than 5 to 10% of the body. Topical therapy help provide symptomatic relief, minimize required doses of systemic medications (if being used) and may also be psychologically cathartic for some patients.[10] Treatment options for mild-to-moderate disease include topical corticosteroids, emollients, tar, topical retinoids and the vitamin D analogs. Most often, a combination of topical corticosteroids and either calcipotriene, calcitriol or tazarotene are prescribed.[10] Many patients find that certain medications are very messy or difficult to apply. For scalp psoriasis, many patients prefer lotions, solutions, gels, foams, or sprays as vehicles as opposed to creams and ointments.[10]

Table 1. Medications Included Within the Therapeutic Class Review[1-9]

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/ Strength	Generic Availability
Single-Entity Agents			
Calcipotriene (Calcitrene®*, Dovonex®*, Sorilux®)	Treatment of plaque psoriasis (cream, ointment, foam)‖, Treatment of plaque psoriasis of the scalp (foam, solution¶)‖	Cream, Ointment, Solution: 0.005% Foam: 0.01%	✔
Calcitriol (Vectical®*)	Treatment of plaque psoriasis†	Ointment: 3 µg/g	✔
Tazarotene (Tazorac®)	Treatment of plaque psoriasis#, Treatment acne vulgaris (0.1% cream/gel)	Cream: 0.05% 0.1% Gel: 0.05% 0.1%	-
Combination Products			
Calcipotriene/ betamethasone (Taclonex®*, Taclonex Scalp®*)	Treatment of plaque psoriasis‡, treatment of plaque psoriasis of the scalp (suspension)	Ointment: 0.005%/0.064% Suspension: 0.005%/0.064%	✔

*Generic is available in at least one dosage form or strength.

Evidence-based Medicine

- Clinical trials have consistently demonstrated the safety and efficacy of the topical psoriasis agents, calcipotriene, calcitriol and tazarotene either alone or in combination.[14-56]
- Calcipotriene monotherapy is an effective and safe treatment for the management of psoriasis and studies have evaluated its effectiveness versus placebo, coal tar and betamethosone.[14-19]
    - Calcipotriene was also found to be safe and effective for the treatment of scalp psoriasis.[20-22]
- The combination of calcipotriene and betamethasone was more effective than placebo or monotherapy with either agent alone at treating the signs and symptoms of psoriasis.[23-35]
    - The efficacy combination calcipotriene and betamethasone was also seen when treating patients who had a diagnosis of scalp psoriasis.[37-40]
- Calcitriol has been shown to be an effective treatment option for patients with psoriasis.[41-45]
- Tazarotene has been shown to be as effective as clobetasol and coal tar in several clinical trials.[46-48]
- There have been several head-to-head studies evaluating the safety and efficacy of these agents. When calcipotriene is compared to calcitriol as monotherapies or in combination with a corticosteroid, the results of trials regarding "superiority" are conflicting, but suggest that both agents are effective.[50-53]
    - One study found that calcitriol is better tolerated that the calcipotriene, with perilesional erythema (P<0.001), perilesional edema (P<0.02) and stinging/burning (P<0.001) all less severe with calcitriol than with calcipotriol.[53]
- Tazarotene plus mometasone was compared to calcipotriene monotherapy and was shown to be not significant different in the percentage of patients achieving complete or almost complete clearance at any time during eight weeks of treatment.[54]
    - Two other studies comparing calcipotriene to tazarotene were done and showed similar results.[55-56]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Potent corticosteroids are recommended as first-line treatment for mild/moderate plaque psoriasis they have well documented efficacy and well known safety profile.[11-12]
    - For psoriasis not responsive to a potent steroid and treatment is required longer than four to eight weeks (depending on potency of steroid), topical vitamin D analogs, tazarotene and other agents such as coal tar can be used.
    - Special considerations need to be made depending on the location and severity of the disease. For areas of the face, flexures and genitals, which are highly sensitive to steroid atrophy, a short term of mild or moderate potency corticosteroids are recommended for a short period of time (two weeks maximum).[11]
    - For moderate to severe plaque psoriasis requiring systemic therapy, topical agents can be used as an adjunctive therapy to help with the signs and symptoms of the disease.[13]
- Other Key Facts:
    - Tazarotene is currently the only agent with no generic available; although, calcipotriene foam (Sorilux®) is also only available as a branded medication.

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Therapeutic Class Review
Topical Psoriasis Agents

Overview/Summary

The focus of this review will be the topical agents used for the treatment of psoriasis.[1-9] These agents include the vitamin D analogs calcipotriene and calcitriol along with the retinoid tazarotene. Calcipotriene is also formulated with betamethasone in a combination product. Each of these medications are Food and Drug Administration (FDA) approved for the treatment of plaque psoriasis. Certain calcipotriene products also have the indication for treatment of scalp psoriasis. In addition to psoriasis, tazarotene is approved for the treatment of acne vulgaris, however its use for this indication will not be included in this review.[1-9] The exact mechanisms of action of the vitamin D analogs and topical retinoids is unknown. The vitamin D analogs are believed to involve the drug's ability to inhibit keratinocyte proliferation and stimulate keratinocyte differentiation.[10] The activated tazarotene binds to all three members of the retinoic acid receptor (RAR) family: RARα, RARβ, and RARγ, but shows relative selectivity for RARβ, and RARγ and may modify gene expression. The clinical significance of this is unknown.[8,9]

Psoriasis is a common chronic skin disorder typically characterized by erythematous papules and plaques with a silver scale, although other presentations occur. Most cases are not severe enough to affect general health and are treated in the outpatient setting.[10] The options for treatment are topical or systemic and depend on the severity of the disease. Mild-to-moderate disease can often be managed with topical agents, while patients with moderate-to-severe disease may need systemic therapy. Moderate-to-severe disease is usually considered to effect more than 5 to 10% of the body. Topical therapy helps provide symptomatic relief, minimize required doses of systemic medications (if being used) and may also be psychologically cathartic for some patients.[10] Treatment options for mild-to-moderate disease include topical corticosteroids, emollients, tar, topical retinoids and the vitamin D analogs. Most often, a combination of topical corticosteroids and either calcipotriene, calcitriol or tazarotene are prescribed.[10] Severe disease is often managed with systemic retinoids, methotrexate, cyclosporine, or biologics.[10] Scalp psoriasis is more difficult to treat due to the presence of hair. Many patients find that certain medications are messy or difficult to apply. For scalp psoriasis, many patients prefer lotions, solutions, gels, foams, or sprays as vehicles as opposed to creams and ointments.[10] Current clinical guidelines usually recommend potent corticosteroids as the first line to well documented efficacy and well known safety profile. Topical vitamin D analogs, tazarotene and other agents such as coal tar can be used first line, but are especially recommended when there is treatment failure on corticosteroids or patients require long-term (greater than four to eight weeks of therapy).[11,12] Special considerations need to be made depending on the location and severity of the disease. For areas of the face, flexures and genitals, which are highly sensitive to steroid atrophy, mild or moderate potency corticosteroids are recommended for a short period of time (two weeks maximum).[11] For moderate to severe plaque psoriasis requiring systemic therapy, topical agents can be used as an adjunctive therapy to help with the signs and symptoms of the disease.[13]

Calcipotriene is formulated as a cream, ointment, solution and foam by itself and as an ointment and suspension when formulated with betamethasone. Calcitriol is only available topically as an ointment. Tazarotene is available as either a cream or gel. Tazarotene is currently the only agent without a generic available; although, calcipotriene foam (Sorilux®) is also only available as a branded medication.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single Agent Products		
Calcipotriene (Calcitrene®*, Dovonex®*, Sorilux®)	Topical Vitamin D analog	✔
Calcitriol (Vectical®*)	Topical Vitamin D analog	✔
Tazarotene (Tazorac®)	Topical Retinoid	-
Combination Products		
Calcipotriene/betamethasone (Taclonex®*, Taclonex Scalp®*)	Topical Vitamin D analog/ topical glucocorticoid	✔

*Generic is available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration Approved Indications[1-9]

Indication	Single Agent Products			Combination Products
	Calcipotriene	Calcitriol	Tazarotene	Calcipotriene/ betamethasone
Treatment of plaque psoriasis	✔* (cream, ointment, foam)	✔†	✔#	✔‡
Treatment of plaque psoriasis of the scalp	✔* (foam, solution¶)			✔ (suspension)
Treatment of acne vulgaris			✔ (0.1 % cream/gel)	

*The safety and effectiveness of topical calcipotriene in dermatoses other than psoriasis have not been established.
†Mild to moderate plaque psoriasis.
‡Ointment: psoriasis vulgaris.
#Gel formulation: stable plaque psoriasis of up to 20% body surface area involvement.
§Facial acne vulgaris of mild to moderate severity. Treatment of acne previously treated with other retinoids or resistant to oral antibiotics has not been established.
¶Chronic, moderately severe psoriasis of the scalp.

Potential off-label uses for donepezil include autism, vascular dementia, poststroke aphasia and improvement of memory in multiple sclerosis patients. Rivastigmine capsules have been used off-label for the treatment of the behavioral symptoms in Lewy-body dementia.[10]

Pharmacokinetics

Table 3. Pharmacokinetics[4-12]

Generic Name(s)	Bioavailability (%)	Metabolism (%)	Excretion (%)	Serum Half-Life (hours)
Single Agent Products				
Calcipotriene	Minimal to 6	Liver	Not reported	Not reported
Calcitriol	Not reported	Kidney	Renal	5 to 8
Tazarotene	2 to 3	Liver	Renal, Bile	18
Combination Products				
Calcipotriene/betamethasone	Not reported	Liver	Not reported	Not reported

Clinical Trials

Clinical trials have consistently demonstrated the safety and efficacy of the topical psoriasis agents, calcipotriene, calcitriol and tazarotene either alone or in combination.[14-56] The majority of the studies compared these agents to placebo or active comparators in other classes, such as topical glucocorticoids; however, there have been several head-to-head trials that have evaluated the efficacy of different agents within the class.[50-56]

Calcipotriene monotherapy is an effective and safe treatment for the management of psoriasis and studies have evaluated its effectiveness compared to placebo, coal tar and betamethosone.[14-19] The clinical trials involving coal tar involved different patient populations and treatment regimens and, although each trial shows calcipotriene to be safe and effective, the trials have yielded mixed results regarding "superiority" of one agent over another.[15-17] Two trials included betamethasone as an active comparator compared to calcipotriene, one of which specifically evaluated psoriasis of the nail bed. Both trials showed safe and effective reduction of psoriasis symptoms for both agents, with similar effects.[18,19] Calcipotriene was also found to be safe and effective for the treatment of scalp psoriasis.[20-22] One study compared calcipotriol to clobetasol for the treatment of scalp psoriasis found the clobetasol propionate was significantly more efficacious compared to calcipotriol in Total Severity Score (TSS) measures ($P<0.001$ at week two and $P=0.028$ at week four) and Global Severity Score (GSS) measures ($P<0.001$ at week two and $P=0.016$ at week four).[22]

The combination of calcipotriene and betamethasone was more effective than placebo or monotherapy with either agent alone at treating the signs and symptoms of psoriasis.[23-35] A single study evaluated the combination product to clobetasol and showed after four weeks of therapy, there was no significant difference in treatment success (clear or mild as assessed using the investigator global assessment scale) among the groups (73% for clobetasol vs 65% for calcipotriene and betamethasone; P value not reported).[40] The efficacy combination calcipotriene and betamethasone was also seen when treating patients who had a diagnosis of scalp psoriasis.[37-40]

Calcitriol has also been shown to be an effective treatment option for patients with psoriasis in several clinical trials.[41-45] When compared to betamethasone monotherapy, there was no significant differences in total clearance of lesions, global improvement scores, similar decrease in the mean GSS and improved Psoriasis Area Severity Index (PASI).[44] When calcitriol was compared to tacrolimus, the mean Toronto Alexithymia Scale (TAS) significantly decreased for both groups (51.4% and 63.8%, respectively). Tacrolimus was significantly more effective than calcitriol at week four and at the end of the six-week treatment period ($P<0.05$).[45]

Tazarotene has been shown to be as effective as clobetasol and coal tar in several clinical trials.[46-48] A single study evaluated the combination of tazarotene and calcipotriene compared to clobetasol. At the end of the two week treatment period, both the tazarotene plus calcipotriene group and the clobetasol group showed marked reductions in scaling, plaque elevation, and overall lesional severity ($P<0.0001$). There were no significant differences in these parameters between groups.[49]

There have been several head-to-head studies evaluating the safety and efficacy of these agents. When calcipotriene was compared to calcitriol as monotherapy or in combination with a corticosteroid, the results of trials regarding "superiority" are conflicting, but suggest that both agents are effective.[50-53] One study found that calcitriol is better tolerated that the calcipotriene, with perilesional erythema ($P<0.001$), perilesional edema ($P<0.02$) and stinging/burning ($P<0.001$).[53] Tazarotene plus mometasone was compared to calcipotriene monotherapy and was shown to be not significantly different in the percentage of patients achieving complete or almost complete clearance at any time during eight weeks of treatment.[54] Two other studies comparing calcipotriene to tazarotene showed similar results.[55-56]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Psoriasis				
Feldman et al[14] Calcipotriene 0.005% foam BID vs vehicle foam (Two studies reported of identical design).	DB, MC, PG, RCT Patients ≥12 years of age with plaque psoriasis involving 2 to 20% of BSA	N=529 8 weeks	Primary: Treatment success defined as change from baseline at week eight of at least two grades and an ISGA score of 0 or 1 Secondary: Change from baseline in ISGA score, ISGA score of 0 or 1, target lesion score of 0 or 1 for erythema and at least a 2-grade improvement from baseline, target lesion score of 0 or 1 for scaling and at least a 2-grade improvement from baseline, a target lesion score of 0 for plaque psoriasis, and adverse effects	Primary: In Study 1, 14% of the calcipotriene group achieved treatment success compared to 7% in the vehicle group (P=0.058). In Study 2, there was a significantly greater proportion of patients that achieved treatment success in the calcipotriene group compared to placebo (P=0.016). Secondary: In Study 1, there was no significant difference in the proportion of patients with mild severity (ISGA scores of 2) who achieved treatment success between the two groups (3 vs 9%; P=0.167). For patients with moderate disease severity (ISGA score of 3), the treatment success rate was significantly higher in the calcipotriene group compared to vehicle (19 vs 6%; P=0.009). In Study 2, there was no significant difference in the proportion of patients with mild severity (ISGA scores of 2) who achieved treatment success between the two groups (14% vs 13%; P=0.859). For patients with moderate disease severity (ISGA score of 3), the treatment success rate was significantly higher in the calcipotriene group compared to vehicle (32 vs 17%; P=0.015). For Study 1, the secondary endpoints for IGSA score of 0 or 1, target lesion score for erythema, scaling, and psoriasis were not considered significant because the primary endpoint failed to reach significance. For Study 2, the proportion of patients with target lesion score of 0 or 1 and grade-2 improvement in the calcipotriene group compared to vehicle was significantly greater for erythema (P=0.034), scaling (P=0.004), but not plaque thickness (P=0.052). A similar proportion of patients in the calcipotriene group experienced adverse effects compared to the vehicle group (16 vs 18%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Veronikis et al[15] Calcipotriene applied BID vs coal tar 1% emulsion applied BID	CS, SB Patients 18 to 75 years of age with plaque-type psoriasis	N=20 12 to 125 days	Primary: Erythema, scaling, and plaque thickness Secondary: Not reported	Primary: The scores for erythema, scaling, and plaque thickness significantly decreased in both the calcipotriene group and the coal tar group (P<0.05), though there were no significant differences observed between treatment groups. Secondary: Not reported
Alora-Palli et al[16] Calcipotriene 0.005% cream applied BID vs liquor carbonis distillate (LCD) 15% solution (equivalent to 2.3% coal tar) applied BID	RCT Patients ≥18 years of age with moderate, chronic plaque psoriasis	N=60 Treatment: 12 weeks Follow-up: 6 weeks	Primary: Change in PASI Secondary: Change in PGA scale score, Pruritus Scale score, DLQI, and patient-reported psoriasis symptoms score Secondary: Not reported	Primary: After 12 weeks, mean PASI scores improved by 58% in the LCD group and by 37% in the calcipotriene group (P<0.05). Significantly more patients in the LCD group achieved PASI 50 than in the calcipotriene group (P<0.05). Secondary: The LCD group had more patients (14/27) with absent or minimal psoriasis on the PGA scale than the calcipotriene group (6/28) by the end of treatment (P<0.05). Patients' DLQI scores, Pruritus Scale scores, and patient's scores for flaking/scaling, itch, redness/irritation, burning sensation, roughness/texture, and overall discomfort improved with both treatments (P<0.05 vs baseline). Improvement in redness/irritation was more pronounced in the LCD group (52%) than in the calcipotriene group (29%; P<0.05). Significantly fewer patients in the LCD group than in the calcipotriene group lost their PASI 50 response at week 18 after six weeks without treatment (P<0.05) or had PGA scores at week 18 worsen to pre-treatment severity (P<0.01). Between week 12 and week 18, PASI scores and PGA scores worsened after stopping calcipotriene therapy (P<0.05), but not after stopping LCD therapy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Patients' Pruritus Scale scores worsened after stopping calcipotriene therapy (P=0.006) but not after stopping LCD therapy (P=0.28). This difference was significant between treatment groups (P=0.003). Patients' DLQI scores improved after stopping LCD therapy (P=0.03), but worsened directionally after stopping calcipotriene therapy (P=0.13). This difference was significant between treatment groups (P=0.009). Patients scores for scaling/flaking, redness/irritation, itch, and roughness/texture worsened after stopping calcipotriene therapy (P<0.05), but not after stopping LCD therapy. More LCD- than calcipotriene-treated patients considered their psoriasis to be stabilized or improved after 6 weeks without treatment. Patients' assessments of convenience, tolerability and overall opinion of LCD solution and calcipotriene cream were comparable and favorable for both products. Secondary: Not reported
Sharma et al[17] (2003) Calcipotriol 0.005% ointment applied BID vs coal tar 5% ointment applied QHS	RCT, SB Patients 16 to 60 years of age with nearly bilaterally symmetrical lesions of stable plaque psoriasis	N=36 12 weeks	Primary: Improvements in the ESI of psoriatic lesions, relapse rates, and self-assessment by patient of efficacy and acceptability Secondary: Not reported	Primary: At four weeks, there was a significant improvement (>50% reduction in ESI score) in 60% of patients on the calcipotriol side compared to 23.3% of patients on the coal tar side (P<0.01). At eight weeks, there was a significant improvement (>505 reduction in ESI score) in 73.3% of patients on the calcipotriol side compared to 33.3% of patients on the coal tar side (P<0.01). At eight weeks, there was a marked improvement (>75% reduction in ESI score) in 26.6% of patients on the calcipotriol side compared to 0% of patients on the coal tar side. At 12 weeks, there was a marked improvement (>75% reduction in ESI score) in 53.3% of patients on the calcipotriol side compared to 33.3% of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				patients on the coal tar side (P<0.01). At 12 weeks, there was a significant improvement observed in 86.7% of patients for both calcipotriol and coal tar. The median time for attaining a >50% reduction in ESI score for calcipotriol was 6.1±1.9 weeks and 9.6±1.8 weeks for coal tar (P<0.01). During the eight week follow-up period, relapse was observed in 10% of patients on the calcipotriol side compared to 16.7% of patients on the coal tar side, though this difference was not significant (P>0.05). There was no significant difference between the physician and patient assessments of degree of improvement at any time during the study. There was a preference for calcipotriol ointment for visual presentability, lack of staining, and cosmetic elegance compared to coal tar. Secondary: Not reported
Tosti et al[18] Calcipotriol 50 µg/g ointment applied BID vs betamethasone 64 mg/g ointment and salicylic acid 0.03 g/g ointment applied BID	DB, RCT Patients ≥18 years of age with a diagnosis of nail bed psoriasis with severe subungual hyperkeratosis	N=58 3 months with an optional additional 2 months of treatment for responders	Primary: Nail thickness expressed in millimeters using a micrometer caliper, patient assessment of acceptability of treatment Secondary: Not reported	Primary: For fingernail psoriasis, subungual hyperkeratosis was reduced by 26.5% in the calcipotriol group and by 30.4% in the betamethasone and salicylic acid group after three months and the difference between groups was not significant. Eight patients in the calcipotriol group and 10 patients in the betamethasone and salicylic acid group were considered responders (>50% reduction in subungual hyperkeratosis in at least one nail). At five months, responders showed a 49.2% reduction in hyperkeratosis in the calcipotriol group and 51.7% reduction in the betamethasone and salicylic acid group (P<0.001). For toenail psoriasis, hyperkeratosis was reduced by 20.1% in the calcipotriol group and 22.9% in the betamethasone plus salicylic acid group at three months (P<0.001 from baseline), but the differences between groups were not significant. Seven patients in the calcipotriol group were considered responders and 12 in the betamethasone and salicylic acid

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				group (>50% reduction in subungual hyperkeratosis in at least one nail). At five months, there was a further reduction in hyperkeratosis in the calcipotriol group (40.7%) and in the betamethasone and salicylic acid group (51.9%) from baseline (P<0.0001 for both groups, between-group differences not reported). Differences in patient assessment of the acceptability of their treatment at three and five months were not significant between groups. Secondary: Not reported
Crosti et al.[19] Calcipotriol 50 µg/g ointment applied BID vs betamethasone dipropionate ointment and salicylic acid ointment applied BID	RCT Patients ≥18 years of age with mild stable psoriasis	N=160 Treatment: 6 weeks Follow-up 1 month	Primary: Improvement in PASI scores, investigator assessments of efficacy Secondary: Not reported	Primary: At the end of the study period, trunk lesions had disappeared in 21.3% of calcipotriol patients and 16.3% of betamethasone and salicylic acid patients, lesions on the arms had disappeared in 21.3% of calcipotriol patients and 15.0% of betamethasone and salicylic acid patients, and lesions on the legs had disappeared in 13.8% of calcipotriol patients and 10.0% of betamethasone and salicylic acid patients. These differences were significant compared to baseline (P<0.05), but not significant between groups. Erythema of the trunk disappeared in 21.3% of calcipotriol patients and 17.5% of betamethasone and salicylic acid patients, erythema of the arms disappeared in 25.0% of calcipotriol patients and 16.3% of betamethasone and salicylic acid patients, and erythema of the legs disappeared in 20.0% of calcipotriol patients and 12.5% of betamethasone and salicylic acid patients. These differences were significant compared to baseline (P<0.01), but not significant between groups. Skin infiltration on the trunk disappeared in 30.0% of calcipotriol and betamethasone and salicylic acid patients, skin infiltration on the arms disappeared in 55.0% of calcipotriol patients and 56.2% of betamethasone and salicylic acid patients, and infiltration on the legs disappeared in 42.5% of calcipotriol patients and 36.3% of betamethasone and salicylic acid

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				patients. These differences were significant compared to baseline (P<0.01), but not significant between groups. Exfoliation on the trunk disappeared in 48.8% of calcipotriol patients and 41.3% of betamethasone and salicylic acid patients, scales on the arms disappeared in 61.3% of calcipotriol patients and 55.0% of betamethasone and salicylic acid patients, and scales on the legs disappeared in 23.8% of calcipotriol patients and 37.5% of betamethasone and salicylic acid patients. These differences were significant compared to baseline (P<0.01), but not significant between groups. By 6 weeks of treatment, PASI scored decreased 66.8% in the calcipotriol patients and 60.8% of betamethasone and salicylic acid patients compared to baseline (P<0.001). Significance for the between-group differences was not reported. Investigators assessed 79% of patients in the calcipotriol group and 89.4% of patients in the betamethasone and salicylic acid group as improved or healed. Treatment acceptability was assessed as “good” or “excellent” by 83.8% of patients in the calcipotriol group and 76.3% of the betamethasone and salicylic acid group. Significance for the between-group differences was not reported. Secondary: Not reported
Feldman et al[20] Calcipotriene 0.005% foam BID vs vehicle foam	DB, MC, PG, RCT Patients ≥12 years of age with plaque psoriasis involving 3 to 10% of total BSA (excluding scalp and face), with an ISGA of 3 at	N=363 8 weeks	Primary: Proportion of patients with ISGA score of 0 or 1 for scalp involvement at week eight Secondary:	Primary: A significantly greater proportion of patients in the calcipotriene group had an ISGA score of 0 or 1 for scalp involvement compared to vehicle (40.9 vs 24.2%; P<0.001). Secondary: At week eight, there was no significant difference in the proportion of patients with an ISGA score of 0 or 1 for total body involvement between the groups (P=0.544).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	baseline, target lesion of >2 cm^2 on the trunk or extremities with a score of 2 or 3 for erythema, scaling and plaque thickness and plaque psoriasis on ≥10% of the total scalp surface area with an ISGA score of 3 at baseline		Proportion of patients with ISGA score of 0 or 1 for body involvement at week eight; target lesion score of 0 or 1 for erythema, sling and plaque thickness; and an improvement of ≥2 grades; primary and secondary endpoints at weeks two and four	At week eight, there was no significant difference in the proportion of patients that achieved an ISGA score of 0 or 1 and an improvement of ≥2 grades for target lesion erythema (P=0.112), scaling (P=0.059) or plaque thickness (P=0.116). At weeks two and four, there were a significantly greater proportions of patients in the calcipotriene group that achieved an ISGA score of 0 or 1 for scalp psoriasis compared to vehicle (P=0.41 and P<0.001, respectively), scaling (P=0.02 and P=0.015, respectively). At week four, there was a significantly greater proportion of patients in the calcipotriene group that achieved an ISGA score of 0 or 1 and an improvement of ≥2 grades for target lesion erythema (P<0.001) and plaque thickness (P=0.036), but not at week two (P=0.895 and P=0.268, respectively). The mean percent reduction in the percent of scalp affected by psoriasis was significantly greater in the calcipotriene patients compared to vehicle at week four (P=0.017) and eight (P=0.002), but not at week two (P=0.159). There was a higher incidence of treatment related adverse events with calcipotriene compared to vehicle (17 vs 7%). The most common adverse event was application site reactions.
Thaci et al[21] Calcipotriol 50 µg/mL solution applied BID as monotherapy or in combination with other treatments	OS, PRO Patients 30 to 62 years of age with scalp psoriasis	N=3,396 8 weeks	Primary: Investigator assessment of psoriasis severity based on the PSSI at each visit, investigators' global assessments of	Primary: There was a significant decrease in mean PSSI after eight weeks of therapy in the group treated only with calcipotriol solution from 16.0 to 4.9 and in the patients treated with calcipotriol solution in combination with other agents from 20.7 to 6.2 (P<0.001). There was an additional therapeutic effect noted in patients treated with calcipotriol solution in combination with selective ultraviolet phototherapy and topical corticosteroids (P<0.001 and P<0.01 respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			changes in psoriasis, tolerance, and cosmetic acceptance of the treatment, and investigator and patient comparison of this therapy to previous therapies Secondary: Not reported	Investigators rated the improvements to be very good or good in 79.8% of patients. Among patients, 75.7% rated the improvements to be very good or good, 91.7% rated the treatment to be very well or well tolerated, and 95.8% rated the cosmetic acceptance to be very good or good. Investigators rated calcipotriol solution to be more effective than past treatments in 45.1% of patients. Safety was rated as improved by 32.4% of patients compared to past treatments. Application of the product was rated easier by 36.8% of patients. Calcipotriol was rated cosmetically more acceptable than previous treatments by 45.1% of patients. There were no major differences between investigator and patient global assessments. Secondary: Not reported
Reygagne et al[22] Calcipotriol 0.005% solution applied BID vs clobetasol 0.05% shampoo applied QD	MC, PG, RCT, SB Patients ≥12 years of age with moderate to severe scalp psoriasis	N=151 4 weeks	Primary: GSS and theTSS Secondary: Pruritus, surface area of scalp affected by psoriasis	Primary: Clobetasol propionate was shown to be significantly more efficacious compared to calcipotriol in TSS measures (P<0.001 at week two and P=0.028 at week four) and GSS measures (P<0.001 at week two and P=0.016 at week four). Secondary: Erythema, plaque thickening, adherent desquamation, and pruritus improved in both treatments groups but a greater improvement was observed in the clobetasol group. The percentage of scalp surface area affected showed significant difference in favor of clobetasol (P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Parslew et al[23] Calcipotriene and betamethasone dipropionate applied QD vs placebo	MA Patients ≥18 years of age with a diagnosis of psoriasis vulgaris	N=1,534 (4 trials) Up to 4 weeks of treatment	Primary: Percent change in PASI Secondary: PASI after one week of treatment (assessed in three of the four studies), IGA	Primary: The mean PASI at baseline was 10.2 in patients <60 and 9.7 in patients ≥60. The mean reduction in PASI was 67.8% in patients <60 and 72.6% in patients ≥60. Secondary: More than half of the treatment response was seen after the first week of treatment with a 39% reduction in PASI in patients <60 and a 40.75 reduction in patients ≥60. In the two studies assessing IGA of Disease Severity, 52.1% of patients <60 and 52.8% of those ≥60 had controlled disease after up to four weeks of treatment. A total of 59% of patients <60 and 64.4% of those ≥60 judged themselves as having attained treatment success. A similar portion of patients <60 and ≥60 experienced lesional or perilesional adverse reactions during the study.
Menter et al[24] Calcipotriene 50 µg/g and betamethasone dipropionate 0.5 mg/g suspension vs betamethasone dipropionate 0.5 mg/g suspension vs calcipotriene 50 µg/g suspension	DB, MC, RCT Patients ≥18 years of age with mild to moderate psoriasis for ≥6 months involving ≥10% of the arms, legs or trunk and amenable to treatment with ≤100 g of medication per week	N=1,152 8 weeks	Primary: Proportion of patients achieving controlled disease (IGA score of clear or almost clear and ≥2 point change from baseline) at weeks four and eight Secondary: Change from baseline in PASI at weeks four	Primary: At week four, there was a significantly greater proportion of patients achieving controlled disease in the calcipotriene and betamethasone group (13.3%) compared to calcipotriene groups (5.2%; P=0.019) and vehicle (2.1%; P=0.001). There was no significant difference in achievement of controlled disease between the calcipotriene and betamethasone and betamethasone groups (12.5%; P=0.82). At week eight, the calcipotriene and betamethasone group had a significantly greater proportion of patients achieving controlled disease (29%) compared to the betamethasone (21.5%), calcipotriene (14.6%) and vehicle groups (6.3%; P≤0.008 for all comparisons). Secondary: At week four, the calcipotriene and betamethasone group had a significantly greater mean reduction in PASI (46.4%) compared to the betamethasone (42.7%), calcipotriene (32.2%) and vehicle groups (17.4%; P≤0.038 for all

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs vehicle suspension			and eight	comparisons). At week eight, the calcipotriene and betamethasone group had a significantly greater mean reduction in PASI (55.8%) compared to the betamethasone (48.6%), calcipotriene (43.6%) and vehicle groups (20.9%; P<0.001) for all comparisons).
Singh et al[25] Calcipotriene 0.005% ointment applied BID on weeks 2 and 4 and augmented betamethasone 0.05% cream applied QD on weeks 1 and 3 vs augmented betamethasone 0.05% cream applied QD for 4 weeks	PG, RCT, SB Patients 20 to 50 years of age with stable plaque psoriasis	N=52 4 weeks	Primary: Proportion of patients having at least 90% reduction in baseline PASI scores at the end of the four week study period Secondary: PASI scores on a weekly basis, reduction in PASI scores after two to four weeks, patients with marked improvement or almost clear at the end of treatment	Primary: In the betamethasone group, 18.5% of patients had a 90% or greater reduction in baseline PASI scores after four weeks of therapy compared to 68% of patients in the calcipotriene and betamethasone group (P<0.001). Secondary: PASI scores were significantly lower in the calcipotriene and betamethasone group compared to the betamethasone group at different points of time except on days 0 and seven. The percentage reduction in PASI scores after two and four weeks of treatment was significantly higher in the calcipotriene and betamethasone group compared to the betamethasone group. The proportion of patients with marked improvement or who were almost completely cleared at the end of treatment was significantly higher in the calcipotriene and betamethasone group compared to the betamethasone group in both investigator and patient assessments.
Douglas et al[26] Calcipotriene and betamethasone ointment applied BID (CB)	DB, PRO, RCT Patients ≥18 years of age with a diagnosis of psoriasis vulgaris	N=1,106 4 weeks of treatment and an additional 4 weeks of OL treatment	Primary: Mean percent change in PASI from baseline after four weeks Secondary:	Primary: There was a significant reduction in mean percent change in PASI from baseline to week four in the CB group compared to the B group and the C group (74.4, 61.3, and 55.3% respectively; P<0.001). Secondary: There was a significant reduction in mean percent change in PASI after

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs betamethasone ointment applied BID (B) vs calcipotriene ointment applied BID (C)		with calcipotriene	Speed of response as assessed from percent change in PASI after one week, mean percentage decrease in the thickness of psoriatic lesion from baseline after four weeks	week one in the CB group compared to the B group and the C group (47.4, 39.8, and 31% respectively; P<0.001). There was a significant reduction in the mean percent change in thickness of the psoriatic lesion from baseline to week four in the CB group compared to the B group and the C group (79.4, 61.7, and 63% respectively; P<0.001). There was no significant difference in the percent of patients reporting adverse effects in any of the treatment groups.
Kaufman et al[27] Calcipotriene and betamethasone ointment applied QD (CB) vs betamethasone ointment applied QD (B) vs calcipotriene ointment applied QD (C) vs vehicle ointment QD (V)	DB, PC, PRO, RCT Patients ≥18 years of age with a diagnosis of psoriasis vulgaris affecting at least 10% of one or more body regions	N=1,603 4 weeks	Primary: PASI score, IGA score, PGA score assessing patients with treatment success (defined as marked improvement or clearance of disease) Secondary: Not reported	Primary: There was a significant decrease in PASI score in the CB group compared to the B, C, and V groups (-71.3, -57.2, -46.1, and -22.7% respectively; P<0.001). There was a significantly larger number of patients assessed as having controlled disease according to the IGA score in the CB group compared to the B, C, and V groups (276, 176, 107, and 16 respectively; P<0.001). There was a significantly larger number of patients assessed as having treatment success according to the PGA scores after four weeks in the CB group compared to the B, C, and V groups (316, 216, 137, and 15 respectively; P<0.001). Secondary: Not reported
Papp et al[28]	DB, MC, PC, RCT	N=1,028	Primary: Mean percent	Primary: There was a significant percent reduction in PASI at the end of treatment in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Calcipotriene and betamethasone ointment applied BID (CB) vs betamethasone ointment applied BID (B) vs calcipotriene ointment applied BID (C) vs vehicle ointment BID (V)	Patients ≥18 years of age with a diagnosis of psoriasis vulgaris affecting at least 10% of one or more body areas	4 weeks	reduction in PASI from baseline to the end of treatment Secondary: Speed of response assessed as the mean percent change in PASI from baseline after one week of treatment	the CB group compared to the B, C, V groups (73.2, 48.8, 63.1, and 28.8% respectively; P<0.001). Secondary: There was a significant reduction in the mean percent change in PASI from baseline to after one week of treatment in the CB group compared to the B, C, and V groups (48.1, 28.4, 41.4, and 21.5% respectively; P<0.001).
Guenther et al[29] Calcipotriene and betamethasone ointment applied QD vs calcipotriene and betamethasone ointment applied BID vs calcipotriene ointment applied BID	DB, MC, PC, PG, PRO, RCT Patients 18 to 86 years of age with a diagnosis of psoriasis vulgaris involving at least 10% of one or more body regions	N=828 4 weeks	Primary: Percentage change in PASI from baseline to week four Secondary: Percentage change in thickness score of a target psoriatic lesion from baseline to each treatment visit, speed of response	Primary: The difference in PASI from baseline to week four in the combination treatment groups of once and BID was not significant (5.4%; P=0.052). The once-daily combined-medication group had a significantly reduced PASI compared to the calcipotriol group (68.6 vs 58.8%; P<0.001) and the placebo group (68.6 vs 26.6%; P<0.001). The twice-daily combined-medication group had a significantly reduced PASI compared to the calcipotriene group and the placebo group (P<0.001). Secondary: No significant difference was observed between the QD combined-medication group and the calcipotriene group or the once vs BID combined-medication groups in lesion thickness.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			assessed by change in PASI from baseline to week two, investigator's overall assessment of treatment efficacy, adverse effects	There was a significant difference in lesion thickness in the once and BID combination-medication groups compared to the placebo group at the end of treatment (P<0.001). After one week of treatment, the change in PASI was greater in the combined-medication groups (45.5% for QD and 47.6% for BID) compared to the calcipotriene group (33.6%) and the placebo group (20%); (P<0.001). There was no significant difference observed in the speed of response between the QD and BID combination groups (P=0.30). For the investigators' and patients' assessment of efficacy, there was a higher percentage of responders (those achieving marked improvement or clearing) in the QD and BID combination groups (QD: 63.3% investigators, 65.3% patients, BID: 73.5% investigators, 70.1% patients) compared to the calcipotriene group (50.7% investigators, 51.5% patients), and the placebo group (9.2% investigators, 12.6% patients; P<0.033). According to investigators' assessments, 14% of patients receiving the QD and 20.1% of patients receiving the BID combination products achieved clearance compared to 9.7% in the calcipotriene group and 0% in the placebo group. A significantly lower proportion of patients experienced adverse effects in both combination groups compared to the calcipotriene group (P<0.01). The percentage of patients with lesional or perilesional adverse reactions was less in the combination groups and the placebo group compared to the calcipotriene group (9.9% QD combination group, 10.6% BID combination group, 19.8% calcipotriene group, 12.5% placebo group).
van de Kerkhof[30] Calcipotriene and betamethasone ointment applied QD	DB, MC, PC, RCT Patients 18 to 86 years of age with a diagnosis of psoriasis vulgaris	N=828 4 weeks	Primary: Changes in the PDI, EuroQOL 5D, VAS, and the EuroQOL 5D-VAS score	Primary: Results of the PDI scores indicate that patients' QOL improved significantly in both combination groups and the calcipotriene group compared to baseline (P<0.001). No significant effect was seen in the placebo group (P>0.1).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs calcipotriene and betamethasone ointment applied BID vs calcipotriene ointment applied BID vs placebo	involving at least 10% of one or more body regions		from baseline to the end of the study (each of these tools measure overall QOL) Secondary: Not reported	No statistical difference was found in QOL based on PDI score between the combination groups and the calcipotriene group (P>0.1), though a significant difference was noted in favor of the combination groups when compared to the placebo group (P<0.001). At baseline, pain/discomfort and anxiety/depression were the most significant problems reported by psoriasis patients. Parameters for pain/discomfort and anxiety/depression improved to a greater extent in the combination groups than in the calcipotriene and placebo groups. The VAS scores from baseline to the end of the study showed a significant improvement in QOL in both combination groups and the calcipotriene group (P<0.001), and no significant difference was seen in the placebo group from baseline (P>0.1). There was a significant improvement observed in the EuroQOL 5D-VAS score between both combination groups compared to the placebo group (P<0.001), as well as the QD combination group compared to the calcipotriene group (P<0.05). PASI reduction in both combination groups was significantly greater compared to the calcipotriene group and the placebo group after one week (P<0.001). Secondary: Not reported
Kragbale et al[31] Calcipotriene and betamethasone ointment applied QD for 8 weeks followed by calcipotriene ointment applied QD for 4 weeks	DB, PG, PRO, RCT Patients ≥18 years of age with a diagnosis of psoriasis	N=971 12 weeks	Primary: Mean percent change in PASI from baseline to week eight, proportion of patients with absent or very	Primary: There was a significant reduction in the mean percent change in PASI from baseline to week eight in group 1 compared to groups 2 and 3 (73.3, 68.2, and 64.1% respectively; P<0.001). There was a significantly greater percentage of patients with absent or very mild disease in group 1 compared to groups 2 and 3 (55.3, 47.7, and 40.7% respectively; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(Group 1) vs calcipotriene and betamethasone ointment applied QD for 4 weeks followed by calcipotriene ointment applied QD on weekdays and calcipotriene and betamethasone ointment applied QD on weekends for 8 weeks (Group 2) vs calcipotriene ointment applied BID for 12 weeks (Group 3)			mild disease according to the IGA at the end of eight weeks Secondary: Mean percent change in PASI from baseline to each visit and at 12 weeks, proportion of patients with absent/very mild disease according to IGA severity at each visit and at 12 weeks	Secondary: There were no significant differences between the three groups with respect to reduction in PASI scores at week 12. At week 12, significantly more patients in group 2 were assessed as having absent or very mild disease compared to group 3 (P=0.026).
Saraceno et al[32] Calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g applied QD for 4 weeks, followed by calcipotriol 50 µg/g cream applied BID for 8 weeks vs	MC, RCT Patients >18 years of age with mild to moderate plaque psoriasis	N=150 12 weeks	Primary: Changes in the PASI after four weeks of treatment Secondary: Maintenance of the PASI score with calcipotriol as a sequential therapy in the	Primary: A significant improvement of PASI score was demonstrated in patients receiving QD treatment with calcipotriol and betamethasone dipropionate compared to BID treatment with calcipotriol at week two (P<0.001). These results were confirmed and maintained at week four (P<0.001). Secondary: Treatment with calcipotriol from week five to week 12 was associated with a further clinical improvement and treatment with calcipotriol and betamethasone dipropionate was associated with maintenance of the results. At week 12, no significant differences of PASI score were seen between the two groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
calcipotriol 50 µg/g cream applied BID for 12 weeks			following eight weeks; safety of the study drugs; patients' QOL, as assessed by the Skindex-29	The QOL assessment showed a marked improvement in terms of Skindex-29 in both groups at weeks two and four as compared to baseline. Similarly to the clinical improvement, the QOL results were significantly superior in the calcipotriol and betamethasone dipropionate group compared to the calcipotriol group (P<0.001). Treatments were well tolerated. Common side effects included erythema, burning, exacerbation of psoriasis, vesicles, lesional or perilesional irritation, itching.
White et al[33] Calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g ointment for 4 weeks followed by calcipotriol cream 50 µg/g for 8 weeks (cream group) vs calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g ointment for 4 weeks followed by calcipotriol cream 50 µg/g on weekdays and calcipotriol and betamethasone on weekends for 8 weeks (alternating group) vs calcipotriol 50 µg/g and	RCT, SB (4 weeks), DB (8 weeks) Patients ≥18 years of age with a clinical diagnosis of psoriasis vulgaris affecting at least 10% of the arms and/or 10% of the trunk and/or 10% of the legs	N=1136 12 weeks	Primary: Assessment of the PASI, investigators' global assessment of disease severity on a six-point scale (disease absent, very mild, mild, moderate, severe, or very severe), and adverse events Secondary: Not reported	Primary: The mean percentage change in the PASI from baseline to the end of the trial was -44.5% in the calcipotriene cream group, -58.4% in the alternating group, and -33.1% in the vehicle group. The mean difference between the calcipotriene cream and vehicle groups was -11.7% (P<0.001), and the mean difference between the alternating and vehicle groups was -24.7% (P<0.001). For the investigators' global assessment of disease severity at the end of the trial, the differences between the calcipotriene cream and vehicle groups, and between the alternating and vehicle groups demonstrated greater efficacy in the non-vehicle groups (P<0.001). The patients' global assessment of disease severity demonstrated similar results (P<0.001). There were no statistically significant differences in the incidence of adverse drug reactions in the calcipotriene cream group relative to the vehicle group (P=0.21), or in the alternating group relative to the vehicle group (P=0.61). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
betamethasone dipropionate 0.5 mg/g ointment for 4 weeks followed by vehicle cream for 8 weeks (vehicle group)				
Kragballe et al[34] Calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g for 52 weeks vs calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g for 4 weeks followed by calcipotriol 50 µg/g for 4 weeks (alternating for 52 weeks) vs calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g for 4 weeks followed by calcipotriol 50 µg/g for 48 weeks	DB, RCT Patients ≥18 years of age with a clinical diagnosis of psoriasis vulgaris of the trunk and/or limbs	N=634 52 weeks	Primary: Adverse events Secondary: Not reported	Primary: Adverse drug reactions occurred in 21.7% of patients in the calcipotriol and betamethasone group, 29.6% in the alternating group and 37.9% in the calcipotriol group (P<0.001). The OR for an adverse drug reaction in the calcipotriol and betamethasone group relative to the calcipotriol group was 0.46 (95% CI, 0.3 to 0.7; P<0.001). The OR for the alternating group relative to the calcipotriol group was 0.69 (95% CI, 0.46 to 1.04; P=0.073), and for the calcipotriol and betamethasone group relative to the alternating group 0.66 (95% CI, 0.42 to 1.03; P=0.066). Adverse drug reaction of concern associated with long-term topical corticosteroid use occurred in 4.8% of patients in the calcipotriol and betamethasone group, 2.8% of patients in the alternating group and 2.9% of patients in the calcipotriol group. Those adverse drug reaction with the highest incidence were skin atrophy and folliculitis. Secondary: Not reported
van de Kerkhof et al[35] Calcipotriene and betamethasone ointment applied QD	MA Patients ≥18 years of age with a diagnosis of	N=1,534 Up to 4 weeks	Primary: Percent change in PASI from baseline	Primary: Among patients with severe disease at baseline, there was a 71.6% mean reduction in PASI at week four, 68.9% in patients with moderate disease, and 67.2% in patients with mild disease.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	psoriasis vulgaris involving at least 10% of one or more body areas		Secondary: Rate of disease response assessed by the mean reduction in PASI (after week one), patients who achieved treatment success (marked improvement or clearance), and patients with controlled disease (absent or very mild disease) according to IGA and PASI	Secondary: Among patients with severe disease at baseline, there was a 41.2% mean reduction in PASI after week one, 39.3% in patients with moderate disease, and 38.5% in patients with mild disease. Among patients with severe disease at baseline, 44.4% of patients achieved treatment success after four weeks according to IGA, 60.7% in patients with moderate disease, and 63.8% in patients with mild disease. Among patients with severe disease at baseline, 54.2% of patients achieved treatment success after four weeks according to patient's assessments, 60.9% in patients with moderate disease, and 61.2% in patients with mild disease. According to PASI-defined baseline disease severity, 38.7% of patients had controlled disease after four weeks, 52.9% in patients with moderate disease, and 66.1% in patients with mild disease. According to IGA-defined baseline disease severity, 44.1% of patients had controlled disease after four weeks, 53.0% in patients with moderate disease, and 69.3% in patients with mild disease.
Menter et al[36] Clobetasol 0.05% spray applied BID for four weeks vs calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment applied daily for four weeks	MC, RCT Patients 18 to 80 years of age with stable plaque psoriasis involving 3 to 20% of the BSA	N=122 8 weeks	Primary: Efficacy as assessed by ODS, investigator global assessment, PQOL-12 Secondary: Not reported	Primary: After two weeks, 41% of patients receiving clobetasol had treatment success (clear or almost clear) compared to 27% of patients receiving calcipotriene and betamethasone dipropionate. After four weeks, 75% of patients receiving clobetasol were clear or almost clear compared to 45% of patients receiving calcipotriene and betamethasone dipropionate (P=0.003). After eight weeks, 14% of patients receiving clobetasol were clear or almost clear compared to 8% of calcipotriene and betamethasone dipropionate patients. After four weeks, there was no significant difference in treatment success (clear or mild as assessed using the investigator global assessment scale) among the treatment groups (73% for clobetasol vs 65% for calcipotriene and betamethasone dipropionate). After two weeks, 52% of patients receiving clobetasol were clear or mild compared to 33% of patients receiving calcipotriene and betamethasone dipropionate (P=0.054). After

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				eight weeks, 41% of patients receiving clobetasol were clear or mild compared to 24% of patients receiving calcipotriene and betamethasone dipropionate. After four weeks, PQOL-12 scores decreased by 36.1 points with clobetasol and by 30.8 points with calcipotriene and betamethasone dipropionate. After two weeks, PQOL-12 scores decreased by 24.4 points with clobetasol and by 21.4 points with calcipotriene and betamethasone dipropionate. After eight weeks, PQOL-12 scores decreased by 15.9 points with clobetasol and by 10.1 points with calcipotriene and betamethasone dipropionate. Patient satisfaction surveys indicate that more patients were satisfied with clobetasol than with calcipotriene and betamethasone dipropionate. Compliance was similar in both treatment groups (100% for clobetasol and 97% for calcipotriene and betamethasone dipropionate). Erythema, scaling and dryness were similar in both treatment groups. More patients experienced stinging/burning with clobetasol. Secondary: Not reported
Tyring et al[37] Calcipotriene 50 µg/g and betamethasone dipropionate 0.5 mg/g scalp formulation applied QD vs placebo	DB, RCT Patients ≥18 years of age with scalp psoriasis who were Hispanic or Latino and/or Black or African American	N=177 8 weeks	Primary: Proportion of patients with cleared or minimal disease Secondary: Investigator's assessment of clinical signs of scalp psoriasis; patient's global assessment of	Primary: In the calcipotriene and betamethasone group, 71.9% of patients had cleared or minimal disease at week eight by the IGA compared to 40.5% in the placebo group (OR, 3.30; 95% CI, 1.62 to 6.72; P<0.001). Secondary: For total sign score ≤1, thickness of scalp psoriasis absent and patient's global assessment of cleared/very mild), calcipotriene and betamethasone was significantly more effective than placebo (P=0.004, P=0.002 and P=0.004, respectively). For absence of redness and scaliness of scalp psoriasis, the response rate was greater with calcipotriene and betamethasone than placebo (P=0.010 and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			severity of scalp psoriasis	P=0.017, respectively). There were 7.0% of patients in the calcipotriene and betamethasone group with 11 adverse events, compared to 7.9% of patients with four adverse events in the placebo group (OR, 0.88; 95% CI, 0.23 to 3.44; P=1.00).
Luger et al[38] Calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g vs calcipotriol 50 µg/g	DB, MC, RCT Patients with moderate to severe scalp psoriasis	N=869 52 weeks	Primary: Efficacy and safety Secondary: Not reported	Primary: Disease was satisfactorily controlled in 92.3% of visits in the calcipotriol-betamethasone group vs 80.0% in the calcipotriol group (P<0.001). Adverse drug reactions were less frequent in the calcipotriol-betamethasone group compared to the calcipotriol group (17.2 vs 29.5%; P<0.001). Incidences of adverse events possibly associated with long-term corticosteroid use were low in both the calcipotriol-betamethasone (2.6%) and the calcipotriol (3.0%) groups. Secondary: Not reported
van de Kerkhof et al[39] Calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g vs betamethasone dipropionate 0.5 mg/g vs calcipotriol 50 µg/g	DB, MC, PG, RCT Patients with scalp psoriasis involving >10% of the scalp	N=1417 8 weeks	Primary: Proportion of patients with 'absence of disease' or 'very mild disease' according to investigators' assessments Secondary: Patient ratings of scalp psoriasis and adverse events	Primary: The proportion of patients with 'absence of disease' or 'very mild disease' at week eight was significantly higher in the calcipotriol and betamethasone group (68.4%) than the betamethasone dipropionate (61.0%; P=0.0079) or calcipotriol (43.4%; P<0.0001) groups. Secondary: The proportion of patients rating their scalp psoriasis as 'clear' or 'almost clear' was significantly higher in the calcipotriol and betamethasone group (69.6%) than for betamethasone dipropionate (59.9%; P=0.0006) or calcipotriol (44.7%; P<0.0001). The incidence of lesional/perilesional adverse events was lower in the calcipotriol and betamethasone and betamethasone dipropionate groups than the calcipotriol group.
Jemec et al[40] Calcipotriol 50 µg/g and	DB, MC, RCT Patients with scalp	N=1505 8 weeks	Primary: Patients with ‘‘absence of	Primary: The proportion of patients who achieved ‘‘absent’’ or ‘‘very mild’’ disease at week eight was significantly greater in the calcipotriol and betamethasone

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
betamethasone dipropionate 0.5 mg/g applied QD vs betamethasone dipropionate 0.5 mg/g applied QD vs calcipotriol 50 µg/g applied QD vs placebo	psoriasis		disease'' or ''very mild disease'' according to IGA of disease severity at week eight Secondary: Total Sign Score at week eight, proportion of patients who were ''almost clear'' or 'cleared'' by patients' assessment	group (71.2%) compared to the betamethasone dipropionate group (64.0%; P=0.011), the calcipotriene group (36.8%; P<0.0001), and the placebo group (22.8%; P<0.0001). Secondary: At week eight, the percentage change in Total Sign Score was significantly larger for the calcipotriol and betamethasone group (-70.8%) than for calcipotriene (-49.0%; P<0.0001) and for placebo (-35.6%; P<0.001). The difference vs betamethasone dipropionate, (-67.7%) was not statistically significant (P=0.12). The proportion of patients who rated their scalp psoriasis as ''cleared'' or ''almost clear'' at week eight was 68.6% for the calcipotriol and betamethasone group, 62.5% for betamethasone dipropionate, 38.3% for calcipotriene, and 20.7% for the placebo alone. The calcipotriol-betamethasone group was significantly more effective than calcipotriene (P<0.0001) and the placebo alone (P<0.0001). The difference vs betamethasone dipropionate was not statistically significant (P=0.2).
Lebwohl et al[41] Calcitriol 3 µg/g ointment applied BID vs placebo	DB, RCT Patients with mild to moderate chronic plaque psoriasis	N=839 8 weeks	Primary: GSS; safety Secondary: Not reported	Primary: Calcitriol 3 µg/g ointment was significantly more effective than placebo, with onset of therapeutic effect seen as early as week two and sustained at all subsequent visits. Calcitriol 3 µg/g ointment demonstrated good systemic and local safety profile comparable to its placebo with no effect on calcium homeostasis. Secondary: Not reported
Lebwohl et al[42] Calcitriol 3 µg/g ointment applied BID	MC, OL Patients ≥12 years of age with mild to moderate chronic plaque psoriasis	N=324 26 to 52 weeks	Primary: Safety Secondary: Global assessment of improvement	Primary: Adverse events were reported for 40% of patients. The most common adverse events were abnormal laboratory test results, which included elevated blood calcitriol levels (7%), pathological blood PTH and calcitriol levels (0.3%), and elevated blood PTH levels (0.3%). Adverse events thought to be related to study treatment were noted for 45

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				patients (13.9%). Eight patients (2.5%) had adverse events leading to study discontinuation, and adverse events for four of these patients (1.2%) were considered related to treatment. These events included irritant dermatitis, pruritus, kidney pain, and urine abnormality (one patient each). Six patients experienced severe adverse events; none were related to calcitriol treatment. Secondary: At least marked improvement was reported by 131 of 249 patients (52.6%) at week 26 and 83 of 130 patients (63.8%) at week 52. Approximately 21% (52/249) of patients rated themselves as clear or almost clear at week 26 and 30% (39/130) at week 52. Mean percentage BSA decreased over time from 16.1% at baseline to 10.7% at end point.
Langner et al[43] Calcitriol 3 µg/g ointment applied BID	MC, OL Patients ≥18 years of age with chronic plaque-type psoriasis	N=253 78 weeks	Primary: Overall improvement of the treated lesions; PASI score Secondary: Not reported	Primary: Ninety-six (40.1%) patients showed definite or considerable improvement at end-point compared to baseline, and clearance of psoriasis was reported in 39 (16.3%) patients. Forty-six patients who showed clearing or considerable improvement of psoriasis were withdrawn from the study due to this outcome. Eleven (23%) of these patients relapsed within three months and subsequently re-entered the study. From the remaining group of 36 patients, a relapse after 3 months was reported in six patients. The number of patients with severe or very severe psoriasis fell from 120 (47.4%) at baseline to 54 (21.4%) at end-point. The number with none or slight psoriasis increased from 19 (7.5%) to 98 (38.8%). Pruritus showed a significant improvement over the course of the study. At baseline, 4.3% of the patients complained of severe, distressing pruritus, which had fallen to 1.2% at the three- and 12-month assessments. At the start of the study, only 17% of patients had no specific complaint of pruritus, but this had improved to 48.4% at the three-month assessment and 38.7% at end-point.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The PASI score showed a marked improvement after three months treatment (53.2% reduction in score), which was maintained over the whole course of the study. Secondary: Not reported
Camarasa et al[44] Calcitriol 3 µg/g ointment applied BID vs betamethasone dipropionate 0.05% ointment applied BID	DB, MC, RCT Adults with chronic plaque-type psoriasis of at least moderate severity	N=258 Treatment: 6 weeks Follow-up: 8 weeks	Primary: Global improvement of treated psoriatic lesions; PASI; relapse Secondary: Not reported	Primary: After six weeks, both calcitriol and betamethasone were found to be efficacious. Similar proportions of patients (79% in the calcitriol group and 82% in the betamethasone group) showed definite or considerable improvement in their psoriasis, or total clearance of lesions by treatment endpoint. The mean of the global improvement scores at endpoint were similar (2.31 for calcitriol and 2.55 betamethasone; P<0.05). Both treatment groups showed a clinically relevant decrease in the mean GSS which, at endpoint, was 1.58 for the calcitriol group and 1.36 for the betamethasone group (P<0.05). Each treatment also resulted in a marked improvement in the PASI from baseline to endpoint, with the absolute reduction in the mean PASI at endpoint being comparable between the groups (P>0.05). Relapse warranting new treatment within eight weeks of the study endpoint was required in 52% of patients who had been receiving calcitriol, at a mean of 25.3 days post-treatment. In the betamethasone group, relapse was required for 75% of patients at a mean of 23.4 days post-treatment. The proportion of responders remaining in remission at eight weeks post-treatment (48 and 25% for the calcitriol and betamethasone groups, respectively; P<0.01). The two study ointments were similar in terms of cosmetic acceptability. The overall opinion of the ointments by the majority of patients was generally

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				'good' or 'acceptable' (91 and 92%, for the calcitriol and betamethasone groups, respectively). Secondary: Not reported
Liao et al[45] Calcitriol 3 µg/g ointment applied BID vs tacrolimus 0.3 mg/g ointment applied BID	DB, RCT, SC Patients 18 to 70 years of age with chronic plaque psoriasis affecting face or genitofemoral regions	N=50 6 weeks	Primary: Mean reduction of the TAS Secondary: Percent of patients with complete or almost complete clearance based on the PGA score	Primary: The mean TAS significantly decreased by 51.4% for calcitriol, and 63.8% for tacrolimus. Tacrolimus was significantly more effective than calcitriol at week four and at the end of the six-week treatment period (P<0.05). Secondary: During the treatment period, there was no significant difference in the mean global improvement scores for tacrolimus or calcitriol (3.48 vs 2.67; P=0.066). At the end of the study, more patients achieved complete or almost complete clearance in the tacrolimus group compared to the calcitriol group (60 vs 33%; P<0.05).
Rigopoulos et al[46] Tazarotene 0.1 % cream applied QHS for 12 weeks vs clobetasol 0.05% cream applied QHS for 12 weeks	DB, RCT Patients with psoriasis including nail involvement	N=23 24 weeks	Primary: Assessment of pitting, onycholysis, subungual hyperkeratosis and salmon patches using the NAPSI Secondary: Not reported	Primary: There was no significant difference in pitting, onycholysis, subungual hyperkeratosis, or salmon patches between tazarotene and clobetasol after 12 weeks of treatment. Post hoc analysis at the end of the follow-up period (24 weeks) demonstrated clinical improvement for hyperkeratosis with tazarotene compared to clobetasol (P<0.001). All adverse events reported were mild, with the symptoms ameliorating after a few days. All patients in both groups declared satisfaction with the results at the end of the treatment period. Secondary: Not reported
Angelo et al[47]	RCT, SB	N=36	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tazarotene 0.1% cream applied on one side of the body for 12 weeks vs clobetasol 0.05% cream applied on the other side of the body for 12 weeks	Patients with psoriasis and bilateral symmetrical lesions	16 weeks	Assessment of erythema, scaling and induration on a 4-point scale; investigators' overall assessment of psoriasis including extent and severity; treatment success Secondary: Not reported	During the 12-week treatment period, both tazarotene cream and clobetasol cream were associated with reduction in erythema scores from the baseline except at week two where tazarotene showed no improvement. Clobetasol cream was better than tazarotene cream in reducing the erythema throughout the treatment period with statistically significant differences favoring clobetasol over tazarotene at weeks two, four, six and eight. During the 12-week treatment period, both tazarotene and clobetasol creams were associated with reduction in induration scores from baseline. Tazarotene was better than clobetasol in reducing the induration at weeks two, four, 10 and 12. The difference was statistically significant at week two. Both were equally effective at weeks six and eight. During the 12-week treatment period both tazarotene and clobetasol creams were associated with reduction in desquamation scores from baseline except at week two where tazarotene showed no reduction. Clobetasol cream was better than tazarotene cream in reducing the scaling throughout the treatment period with statistically significant differences favoring clobetasol over tazarotene over the entire 12-week treatment period. The overall improvement at weeks two, four six, eight, 10 and 12 for tazarotene was ~20, ~33, ~43, ~53, ~55 and ~58% respectively and for clobetasol was ~33, ~55, ~73, ~78,~95 and ~95% respectively. Statistically significant differences favored clobetasol cream over tazarotene cream over the entire 12-week treatment period. Clobetasol produced higher success rates than tazarotene over the 12-week treatment period. Statistically significant differences favored clobetasol over tazarotene at weeks two and four. Treatment success rate was 100% at week six with clobetasol and was 73% with tazarotene. At week 12, it was 100% with clobetasol and 88% with tazarotene. Secondary: Not reported
Kumar et al[48]	RCT	N=27	Primary: Severity of	Primary: In the per-protocol analysis, the mean percentage reduction in ESI score at

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tazarotene 0.1% gel applied QHS vs crude coal tar 5% (CCT) ointment applied QHS	Patients with chronic stable plaque psoriasis	Treatment: 12 weeks Follow-up: 8 weeks	psoriatic lesions and response to treatment evaluated by ESI Secondary: Not reported	the end of the treatment period was 74.15 and 77.37% with tazarotene and CCT, respectively (P>0.05). With regard to clinical response, marked, moderate, mild and no response was seen in 0, 3.7, 73.3 and 14.8% of patients, respectively, for both treatments at the end of four weeks of treatment. At the end of eight weeks, the corresponding grades of improvement were 3.7, 70.3, 29.9 and 0% for the tazarotene-treated side, and 3.7, 66.6, 29.6 and 0% for the CCT-treated side. At the end of the 12 weeks of treatment, all 27 patients had moderate to marked improvement on both sides. With tazarotene, marked improvement was seen in 40.7% of lesions, and moderate improvement in 59.2%. With CCT, marked improvement was seen in 59.2% and moderate improvement in 40.7%. Side effects were seen in 48.14% of patients treated with tazarotene: mild irritation (four patients), erythema (four), burning sensation (six), itching (one) and dryness and fissuring (two). No side effects were seen in any of the patients treated with 5% CCT. Secondary: Not reported
Bowman et al[49] Tazarotene 0.05% gel and calcipotriene 0.005% ointment applied QAM and calcipotriene ointment applied QHS vs clobetasol 0.05% ointment applied BID	CS, OL, PRO Patients ≥18 years of age with psoriasis vulgaris that was chronically stable for at least 1 month prior to screening with at least 1 bilateral mirror image plaque on the trunk, arms, or legs	N=15 Treatment: 2 weeks Follow-up 4 weeks	Primary: Severity scores for erythema, scaling, and plaque elevation Secondary: Not reported	Primary: At the end of the two week treatment period, both the tazarotene plus calcipotriene side and the clobetasol side showed marked reductions in scaling, plaque elevation, and overall lesional severity (P<0.0001). There were no significant differences in the tazarotene plus calcipotriene side compared to the clobetasol side in the reduction in scaling (P=0.93), plaque elevation (P=0.76), and overall lesional severity scores (P=0.29). Erythema improved significantly more in the clobetasol-treated lesions during the treatment period (P<0.01) but there was no significant difference between the sides during the post-treatment period (P=0.20). Lesional severity scores worsened on both sides during the post-treatment phase. Plaque elevation returned more rapidly on the tazarotene plus

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				calcipotriene side (P<0.01), but scaling, erythema, and overall lesional severity were not significantly different between the two treatments (P>0.05). No treatment-related adverse effects were reported on the clobetasol side. Adverse effects in the tazarotene plus calcipotriene side were mild and did not result in alteration of the treatment schedule for any patient. Secondary: Not reported
Bourke et al[50] Calcitriol 3 µg/g ointment vs calcipotriol 50 µg/g ointment	DB, RCT Patients with moderately extensive chronic plaque psoriasis	N=24 8 week	Primary: Change in the PASI scores Secondary: Not reported	Primary: Mean PASI in patients receiving calcitriol decreased from 13.0 to 8.8 (P<0.05). Mean PASI in patients receiving calcipotriol decreased from 14.9 to 4.7 (P<0.005). The reduction in PASI was significantly greater in the calcipotriol-treated group than in the calcitriol group (P<0.05). Secondary: Not reported
Zhu et al[51] Calcitriol 3 µg/g ointment applied BID vs calcipotriol 50 µg/g ointment applied BID	RCT, SB Patients 18 to 65 years of age with mild to moderate chronic plaque-type psoriasis involving up to 35% of the BSA	N=250 12 weeks	Primary: Global assessment of improvement assessed by the investigator Secondary: Global assessment of improvement assessed by the patient; safety	Primary: At week 12, the mean global improvement score rated by the investigator was 2.27 for calcitriol and 2.22 for calcipotriol (P=NS). Secondary: At week 12, the mean global improvement score rated by the patient was 2.12 for calcitriol and 2.09 for calcipotriol. There was no significant different in the percentage of patients with at least marked improvement with calcitriol (95.7%) compared to calcipotriol (85%; P=NS). The three clinical signs of the disease, plaque elevation, erythema and scaling, were significantly reduced in all treatment groups. Mean DSS decreased from 8.14 at baseline to 1.87 over the 12-week treatment with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				calcipotriol and from 8.10 to 2.54 with calcitriol (P<0.01). The cutaneous safety score as assessed by the investigator was higher with calcipotriol than with calcitriol (mean scores 0.3 vs 0.1), showing a better local tolerance of calcitriol. A total of 11 (8.9%) patients had a score of 2 or 3, corresponding to 'moderate' or 'severe' local reaction with calcipotriol, whereas only one (0.8%) patient had a 'moderate' reaction with calcitriol (P=0.0035).
Lahfa et al[52] Calcitriol 3 µg/g ointment applied QPM and clobetasol 0.05% cream applied QAM vs calcipotriol 50 µg/g ointment applied QPM and clobetasol 0.05% cream applied QAM When the patient's skin had cleared or improved, the steroid was discontinued and monotherapy with calcitriol or calcipotriol started.	MC, RCT, SB Patients with mild to moderate chronic plaque-type psoriasis	N=125 12 weeks	Primary: Investigator's assessment of global improvement Secondary: Patients' assessments of global improvement, PASI, proportion of the BSA affected by psoriasis	Primary: No significant differences between the two regimen groups in the IGA of improvement were detected at any of the study time points (all, P>0.05). The global assessment by investigators at endpoint revealed a successful clinical response (marked improvement, almost clear or clear) for 79% of patients receiving calcitriol compared to 88% of patients receiving calcipotriol. Secondary: At study endpoint, there was complete clearing of psoriasis lesions in 26% of patients in the calcitriol group and in 25% of patients in the calcipotriol group. In each of the treatment groups, the beneficial effect of treatment on the severity of psoriasis was detected by a marked decrease in PASI. No significant differences between the two regimen groups were detected at any of the study time points.
Ortonne et al[53] Calcitriol 3 µg/g ointment applied BID vs	RCT, SB Patients 18 to 70 years of age with mild to moderate chronic plaque	N=75 6 weeks	Primary: Perilesional erythema and edema; Global assessment of improvement	Primary: Perilesional erythema (P<0.001), perilesional edema (P<0.02) and stinging/burning (P<0.001) were all less severe with calcitriol than with calcipotriol. The IGA of local safety showed that calcitriol was better tolerated than

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
calcipotriol 50 µg/g ointment applied BID	psoriasis localized in facial, hairline, retroauricular or flexural areas		Secondary: Not reported	calcipotriol. More patients considered calcitriol better or much better tolerated than calcipotriol (49.3 vs 10.7%, respectively; P<0.0001). Global assessment of improvement from baseline by the investigators was significantly greater for the calcitriol-treated lesions (P<0.02). A total of 44% of patients considered efficacy to be greater on the calcitriol-treated side than on the calcipotriol-treated side, whereas 29% of patients reported the opposite. The patient's global preference showed a significant difference in favor of calcitriol (P <0.02), with 57% of the patients rating calcitriol as being better or much better than calcipotriol. Secondary: Not reported
Tzung et al[54] Tazarotene 0.1% gel applied QHS and petrolatum applied QAM vs calcipotriene 0.005% ointment applied BID	CS, IB, RETRO Patients 12 to 80 years of age with a diagnosis of psoriasis and a total of 50 target lesion pairs	N=19 Treatment: 12 weeks Follow-up 4 weeks	Primary: Severity scores for scaling, plaque elevation, erythema, overall lesion severity, and patient self-reported efficacy Secondary: Not reported	Primary: At the end of the 12-week treatment period, the tazarotene plus petrolatum was as effective as calcipotriol in the reduction of scaling, plaque elevation, erythema, and overall lesion severity. Erythema worsened in the tazarotene plus petrolatum side in week one and reduction of erythema on this side was first observed in week two. The difference in erythema between sides was not significant after eight weeks. Lesion severity scores worsened on both sides during the post-treatment phase, though the tazarotene plus petrolatum side maintained the therapeutic effect significantly better in terms of scaling, plaque elevation, erythema, and overall severity at week 16 (P<0.001, P<0.001, P=0.01, and P=0.007 respectively). Patient-assessed success rates were 74% on the tazarotene plus petrolatum side and 85% on the calcipotriol side, though this difference was not significant (P>0.46). Secondary: Not reported
Schiener et al[55]	CS, IB	N=10	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tazarotene 0.05% gel applied QD and total body narrowband UVB irradiation QD 4 times per week vs calcipotriene 0.005% ointment applied QD plus total body narrowband UVB irradiation QD 4 times per week	Patients with psoriasis	≥4 weeks	PASI Secondary: Not reported	PASI scores decreased on both treatment sides and there was no significant difference between treatment regimens. Complete clearance of the skin was observed after a median of 19 treatment sessions for both treatment regimens. Secondary: Not reported
Guenther et al[56] Tazarotene 0.1% gel applied QHS and mometasone 0.1% cream applied QAM vs calcipotriene 0.005% applied BID	IB, MC, PG Patients with chronic, stable plaque psoriasis affecting 5 to 20% of total BSA	N=120 Treatment: 8 weeks Follow-up: 12 weeks	Primary: Physician-rated measures of efficacy including global improvement, plaque elevation, scaling, erythema, and percentage of BSA involvement; patient-rated assessments including efficacy of study treatment compared to previous therapies,	Primary: Physician-rated assessments: After two weeks of treatment, the percentage of patients achieving marked improvement (≥75% global improvement) was significantly higher in the tazarotene and corticosteroid group compared to the calcipotriene group (45 and 25% respectively; P<0.05). There was no significant difference in the percentage of patients achieving complete or almost complete clearance between the two treatment groups at any time. For trunk lesions, the mean percentage of reduction in plaque elevation was not significant between groups during the treatment phase, but was significantly higher in the tazarotene plus corticosteroid group at the end of treatment and week four of the post-treatment phase (P<0.05). For upper or lower limb lesions, no significant between-group differences in plaque elevations were observed at any point. For trunk lesions, the mean percentage of reduction in scaling was significantly greater in the tazarotene plus corticosteroid group compared to the calcipotriene group at week four of treatment and at week four of the post-treatment phase (P<0.05). For upper or lower limb lesions, no significant between-group differences in scaling were observed at any point.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			comfort of treated skin, outlook for long-term control, and overall impression of treatment Secondary: Not reported	For trunk lesions, the mean percentage of reduction in erythema was significantly greater in the tazarotene plus corticosteroid group compared to the calcipotriene group at week four of treatment and at the end of treatment (P<0.05). For upper or lower limb lesions, no significant between-group differences in erythema were observed at any point. For trunk lesions, the mean percentage of reduction in BSA involvement was significantly greater in the tazarotene plus corticosteroid group compared to the calcipotriene group after two and four weeks of treatment (P<0.01), though no significant differences were observed between groups in the post-treatment phase. For upper limb lesions, the tazarotene plus corticosteroid group had a significantly higher percentage of reduction in percentage of BSA involvement after two and four weeks of treatment compared to the calcipotriene group (P<0.05 at two weeks and P<0.01 at four weeks). No significant differences were observed during the post-treatment phase between groups. For lower limb lesions, significance was only achieved for patients admitted to the post-treatment phase and only at the end-of-treatment visit (P<0.001). Patient-rated assessments: A significantly greater percentage of patients rated their therapy more effective or much more effective than previously-tried therapies in the tazarotene plus corticosteroid group compared to the calcipotriene group (P<0.05). At the end of treatment, 16% of patients in the tazarotene plus corticosteroid group and 9% of patients in the calcipotriene group rated the comfort of their therapy as somewhat comfortable, 42 and 51% rated it as comfortable, and 27 and 25% rated it as very comfortable, respectively (the significance of these findings are not discussed). No significant between-group differences were observed in the percentage of patients who rated their outlook for long-term control as very promising or extremely promising at the end of the 12 week post-treatment phase. Overall impression of treatment favored the tazarotene plus corticosteroid regimen compared to the calcipotriene regimen, however the percentages of patients who rated their impression of therapy as favorable or highly favorable did not differ between groups, except at the 12-week post-treatment visit (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported

Drug regimen abbreviations: BID=two times a day, QAM=once every morning, QD=once-daily, QPM=once every evening
Study abbreviations: AC=active-controlled, CI=confidence interval, CS=comparative study, DB=double-blind, ES=extension study, IB=investigator-blinded, MA=meta-analysis, MC=multicenter, OL=open label, OS=observational study, PC=placebo-controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, SB=single blind, SR=systematic review
Miscellaneous: BSA=body surface area, DLQI=dermatology life quality index, ESI=erythema, scaling and induration, GSS=global severity score, IGA=investigator global assessment, ISGA=investigator global assessment, PASI=psoriasis area severity index, PDI=psoriasis disability index, PSSI=psoriasis scalp severity index, TAS=Toronto Alexithymia scale, TSS=total severity score, VAS=visual analogue scale

Special Populations

Table 5. Special Populations[1-9]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single Agent Products					
Calcipotriene (Dovonex®, Sorilux®)	There were no significant differences in adverse events in the elderly (cream, solution, ointment). Did not include sufficient numbers of elderly; effect is not known (foam). Safety and effectiveness in pediatric patients have not been established.	Not reported	Not reported	C	Unknown; use with caution
Calcitriol (Vectical®)	Did not include sufficient numbers of elderly; effect is not known.	Not reported	Not reported	C	Unknown; use with caution
Tazarotene (Tazorac®)	The safety and efficacy have not been established in the elderly (cream). Did not include sufficient numbers of elderly; effect is not known (gel). The safety and efficacy have not been established in patients <18 years of age with psoriasis, or in patients <12 years of age with acne (cream). The safety and efficacy have not been established in patients <12 years of age (gel).	Not reported	Not reported	X	Yes

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Combination Products					
Calcipotriene/ betamethasone (Taclonex®)	No overall differences in safety or effectiveness were seen in the elderly The safety and efficacy have not been established in patients <12 years of age with scalp plaque psoriasis; the safety and efficacy have not been established in patients <18 years of age with psoriasis vulgaris (suspension). Safety and effectiveness in pediatric patients have not been established (ointment).	Not reported	Not reported	C	Unknown/ Yes

Adverse Drug Events

Table 6. Adverse Drug Events (%)[1-9]

Adverse Event (%)	Single Agent Products			Combination Product
	Calcipotriene	Calcitriol	Tazarotene	Calcipotriene/ betamethasone
Application site reaction (erythema)	2	-	-	-
Application site pain	3	-	-	-
Burning sensation of skin	-	-	-	1 to 1.4
Contact dermatitis	-	-	1 to 10	-
Dermatitis	1 to 10*	-	-	-
Desquamation	-	-	1 to 10	-
Dry skin, irritation	1 to 5†	-	1 to 10	-
Eczema	-	-	1 to 10	-
Erythema	-	-	10 to 23	-
Folliculitis	-	-	-	1 to 1.4
Headache	-	-	-	2.8
Hypercalcemia	-	3	-	-
Hypertriglyceridemia	-	-	1 to 10	-
Nasopharyngitis	-	-	-	2.3

Adverse Event (%)	Single Agent Products			Combination Product
	Calcipotriene	Calcitriol	Tazarotene	Calcipotriene/ betamethasone
Skin irritation	10 to 15*	-	-	-
Peripheral edema	-	-	-	-
Pruritus	1 to 10*	1 to 3	10 to 23	2.8 to 7.2
Rash	1 to 11	-	-	1.2
Skin discomfort	-	3 to 24	-	-
Skin inflammation	-	-	1 to 10	-
Stinging	-	-	1 to 10	-
Transient burning, stinging and tingling	23†	-	-	-
Urine abnormality	-	4	-	-
Worsening of psoriasis	1 to 10	4	10 to 30	1.2 to 3.4

-Not reported or <1%.
✔ No % given.
*Cream formulation only.
†Solution formulation only.

Contraindications

Table 7. Contraindications[1-9]

Contraindications	Parasympathomimetic (Cholinergic Agents)			Central Nervous System Agents, Miscellaneous
	Donepezil	Galantamine	Rivastigmine	Memantine
History of application site reaction with rivastigmine transdermal patch suggestive of allergic contact dermatitis, in the absence of negative allergy testing			✔	
Known hypersensitivity to donepezil hydrochloride or to piperidine derivatives	✔			
Known hypersensitivity to galantamine hydrobromide or any excipients		✔		
Known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation				✔
Known hypersensitivity to rivastigmine, other carbamate derivatives, or other components of the formulation			✔	

Warnings/Precautions

Table 8. Warnings/Precautions[1-9]

Warnings and Precautions	Single Agent Products			Combination Product
	Calcipotriene	Calcitriol	Tazarotene	Calcipotriene/ betamethasone
Allergic contact dermatitis			✔	✔
External use only	✔	✔	✔	
Eye irritation				✔
Flammable; keep away from open flame	✔ *	✔		
HPA-axis effects due to corticosteroids; limit use				✔
Transient irritation of lesions and surrounding uninvolved skin; discontinue if irritation develops	✔		✔	
Hypercalcemia reported, may need to monitor calcium	✔	✔	✔	✔
Hypercalciuria			✔	✔
Ultraviolet light exposure should be minimized	✔	✔	✔	✔

Drug Interactions

Table 9 . Drug Interactions[1-9]

Generic Name	Interacting Medication or Disease	Potential Result
Calcitriol	Drugs that increase serum calcium (e.g., thiazide diuretics)	Caution should also be exercised in patients receiving calcium supplements or high doses of vitamin D.
Tazarotene	Drugs or cosmetics that have a strong drying effect	It is also advisable to "rest" a patient's skin until the effects of such preparations subside before use of tazarotene has begun.

UGT=UDP-glucuronosyltransferase

Dosage and Administration

Calcipotriene should not be used on the face and calcipotriene/betamethasone use on the face, groin or axillae, or if skin atrophy is present at the treatment site.[1-4,8,9]

Table 10. Dosing and Administration[1-9]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single Agent Products			
Calcipotriene	Plaque psoriasis: Cream, foam: apply to the affected area twice daily Ointment: apply to the affected area one to two times daily Scalp psoriasis, moderately severe,	Safety and efficacy in children have not been established.	Cream: 0.005% Foam: 0.01% Ointment: 0.005%

Generic Name	Adult Dose	Pediatric Dose	Availability
	chronic: Solution: apply to the affected scalp area twice daily Plaque psoriasis of the scalp: Foam: apply to the affected area twice daily		Solution: 0.005%
Calcitriol	Mild to moderate plaque psoriasis: Ointment: apply to the affected area twice daily	Safety and efficacy in children have not been established.	Ointment: 3 µg/g
Tazarotene	Acne vulgaris: 0.1% cream, 0.1% gel: apply to the affected area once daily in the evening Plaque psoriasis: Cream, gel: apply to the affected area once daily in the evening	Acne vulgaris in individuals ≥12 years of age: 0.1% formulations: apply to the affected area once daily in the evening	Cream: 0.05% 0.1% Gel: 0.05% 0.1%
Combination Product			
Calcipotriene/ betamethasone	Plaque psoriasis of the scalp and body: Suspension: apply to the affected area once daily; maximum 100 g/week Psoriasis vulgaris: Ointment: apply to the affected area once daily	Plaque psoriasis of the scalp (patients ≥12 years): Suspension: apply to the affected area once daily; maximum, 60 g/week	Ointment: 0.005%/0.064% Suspension: 0.005%/0.064%

Clinical Guidelines

Table 11. Clinical Guidelines

Clinical Guideline	Recommendations
American Academy of Dermatology: **Guidelines of Care for the Management and Treatment of Psoriasis with Topical Therapies (2009)**[11]	• Approximately 80% of patients are affected with mild to moderate psoriasis with the majority of cases able to be successfully treated with topical agents. • Topical agents are also used adjunctively to either ultraviolet light or systemic medications for resistant lesions in patients with more severe disease. • Treatment needs vary depending on body location of disease, characteristics of the psoriasis being treated including lesion thickness, degree of erythema and amount of scaling, as well as patient preferences. • Topical corticosteroids are the cornerstone of treatment for the majority of patients with psoriasis. • Other topical agents include vitamin D analogs, tazarotene, tacrolimus, pimecrolimus, nonmedicated topical moisturizers, salicylic acid, anthralin, coal tar and combination products. • Salicylic acid is a topical keratolytic agent that has been used for many years and has no specific Food and Drug Administration (FDA)-approved indication. • There are no placebo-controlled trials verifying the safety and efficacy of salicylic acid; however, the agent is typically used in combination with other topical therapies. • Coal tar products are often poorly tolerated by patients because of cosmetic issues, including staining of clothes and the tar odor that is present in

Clinical Guideline	Recommendations
	almost all products. • Coal tar is carcinogenic in animals; however, in humans there are no convincing data proving carcinogenicity, and epidemiologic studies fail to show increased risk of skin cancer in patients who use coal tar.
National Institute for Health Care Excellence (NICE): **Psoriasis: The Assessment and Management of Psoriasis (2012)**[12]	• Offer people with psoriasis topical therapy as first-line treatment. o Corticosteroids, vitamin D and vitamin D analogues, dithranol and tar preparations • Offer second-line treatment (ultra violet [UV], methotrexate [MTX], cyclosporine, acitretin) or third-line treatment options (anti-tumor necrosis factor [TNF]α biologics, ustekinumab) at the same time when topical therapy alone is unlikely to adequately control psoriasis: o extensive disease (> 10% of body surface area affected) OR o at least 'moderate' on the static Physician's Global Assessment OR o topical therapy is likely to be ineffective, such as nail disease. • Take into account patient preference, cosmetic acceptability, practical aspects of application and the site(s) and extent of psoriasis to be treated. • Different formulations are recommended for different reasons: o Cream, lotion or gel for widespread psoriasis. o Lotion, solution or gel for the scalp or hair-bearing areas. o Ointment to treat areas with thick adherent scale. • Topical treatment alone may not provide satisfactory disease control, especially in people with psoriasis that is extensive (for example, more than 10% of body surface area affected) or at least 'moderate' on the static Physician's Global assessment. <u>Topical Corticosteroids</u> • Continuous use of potent/very potent corticosteroids may cause: o irreversible skin atrophy and striae o psoriasis to become unstable o systemic side effects when applied continuously to extensive psoriasis (for example, more than 10% body affected). • Aim for a break of four weeks between courses of treatment with potent or very potent corticosteroids. o Consider topical treatments that are not steroid-based (such as vitamin D or vitamin D analogues or coal tar) as needed to maintain psoriasis disease control during this period. • Continuous use of topical corticosteroids limited to four weeks (very potent) or eight weeks (potent) at any site • Do not use very potent corticosteroids in children and young people. <u>Trunk and limb psoriasis in adults</u> • First-line: Offer a potent corticosteroid applied once daily plus vitamin D or a vitamin D analogue applied once daily (applied separately, one in the morning and the other in the evening) for up to four weeks as initial treatment for adults with trunk or limb psoriasis. Maximum of eight weeks. o Additional considerations before changing to the next treatment option should be made. • Second-line: Vitamin D or a vitamin D analogue alone applied twice daily may be effective if there was limited response to combination therapy. • Third line options should be used if no response to twice daily vitamin D or vitamin D analog use for 8 to 12 weeks. o Potent corticosteroid applied twice daily for up to eight weeks OR

Clinical Guideline	Recommendations
	o A coal tar preparation applied once or twice daily. • Fourth line: combination product of calcipotriene and betamethasone once daily for up to four weeks • Offer a very potent corticosteroid in adults with trunk or limb psoriasis only: o in specialist settings under careful supervision o when other topical treatment strategies have failed o for a maximum period of four weeks. • Treatment-resistant psoriasis of the trunk or limbs o Consider short-contact dithranol <u>Trunk and limb psoriasis in children and young people</u> • Consider either o Calcipotriol once daily (for patients six years and older) OR o A potent corticosteroid once daily (for patients one year and older) <u>Scalp psoriasis (all ages)</u> • Initial: Potent corticosteroid applied once daily for up to four weeks • Second line (up to four weeks of therapy with): o A different formulation of the potent corticosteroid for up to four additional weeks AND/OR o Topical agents to remove adherent scale (salicylic acid, emollients and oils) • Third line (up to four to eight weeks of therapy with): o a combined product containing calcipotriol and betamethasone applied once daily for up to four weeks OR o vitamin D or a vitamin D analogue applied once daily (only in those who cannot use steroids and with mild to moderate scalp psoriasis). • Fourth line o Potent corticosteroid applied up to twice daily for two weeks (adults only) OR o coal tar applied once or twice daily. <u>Psoriasis of the face, flexures and genitals (all ages)</u> • These areas are particularly vulnerable to steroid atrophy and that corticosteroids should only be used for short-term treatment of psoriasis. • Offer a short-term mild or moderate potency corticosteroid applied once or twice daily (for a maximum of two weeks). Use care with pediatric patients. • Second line agent required due to failure or continuous use needed: o a calcineurin inhibitor applied twice daily for four weeks. • Do not use potent or very potent corticosteroids on the face, flexures or genitals.
National Psoriasis Foundation: **Consensus Guidelines for the Management of Plaque Psoriasis (2012)**[13]	• This guideline focuses on the management of moderate-severe plaque psoriasis in patients are considered to have moderate to severe psoriasis if they cannot achieve or would not be expected to achieve adequate control using topical agents <u>Topical Therapies</u> • For patients with moderate to severe psoriasis, the topical agents used in mild psoriasis remain useful adjuncts. • Topical calcitriol and tazarotene can be combined with UV treatment. Both of these agents used in combination with NB UV-B can significantly reduce the UV dose needed to achieve clearance.

Clinical Guideline	Recommendations
	Oral therapies • Acitretin is the only antipsoriatic retinoid available for systemic use in the United States. The use of acitretin is limited due to its slow onset of action and persistence of residual plaque psoriasis even when plaque thinning is noted. The combination of acitretin with topical calcipotriene or biological therapy or phototherapy may increase rates of clearance. Acitretin is especially useful in patients with severely sun-damaged skin, in which it may suppress actinic keratoses and even invasive malignant neoplasms. • Although it can be effective in the long term, continuous use of cyclosporine is associated with cumulative renal toxic effects, hypertension and hyperglycemia. Cyclosporine should normally be reserved for intermittent use of no longer than 12 weeks as a short-term treatment agent to control a flare of psoriasis, after which therapy is switched for long-term maintenance. When used in this intermittent fashion, a course of cyclosporine treatment can induce an average decrease of more than 75% in psoriasis severity. • Methotrexate is directly anti-inflammatory because of its effects on T-cell gene expression patterns. Compared to cyclosporine, methotrexate has a more modest effect on psoriasis severity, but can be used continuously for many years with durable benefits. A major safety issue with methotrexate is the cumulative toxic effects to the liver. Biologic agents • Adalimumab may be used as first-line systemic treatment of plaque psoriasis and has a higher efficacy and lower rate of adverse effects compared to methotrexate. • Etanercept is commonly used as a first-line systemic drug for chronic plaque psoriasis. • Infliximab is administered via intravenous infusion, is a fast-acting drug that is often used as a second- or third-line biological for chronic plaque psoriasis • Ustekinumab is associated with favorable results when compared to etanercept in terms of efficacy and safety. It may be used as first-line systemic treatment for chronic plaque psoriasis. • Alefacept is generally used for intermittent use. There is little evidence to support use to achieve full clearance, and it is often used in combination regimens. It may be used as first-line systemic drug for chronic plaque psoriasis.

Conclusions

The topical psoriasis agents include the vitamin D analogs calcipotriene and calcitriol along with the retinoid tazarotene. Calcipotriene is also formulated with betamethasone in a combination product. Each of these medications are Food and Drug Administration (FDA) approved for the treatment of plaque psoriasis. Certain calcipotriene products also have the indication for treatment of scalp psoriasis.[1-9] Current clinical guidelines usually recommend potent corticosteroids as the first line to well documented efficacy and well known safety profile. Topical vitamin D analogs, tazarotene and other agents such as coal tar can be used first line, but are especially recommended when there is treatment failure on corticosteroids or patients require long-term (greater than four to eight weeks of therapy).[11,12] For moderate to severe plaque psoriasis requiring systemic therapy, topical agents can be used as an adjunctive therapy to help with the signs and symptoms of the disease.[13]

Clinical trials have consistently demonstrated the safety and efficacy of the topical psoriasis agents, calcipotriene, calcitriol and tazarotene either alone or in combination.[14-56] The majority of the studies compared these agents to placebo or active comparators in other classes, such as topical glucocorticoids; however, there have been several head-to-head trails that have evaluated the efficacy of different agents within the class.[50-56] When calcipotriene is compared to calcitriol as monotherapies or in combination with a corticosteroid, the results of trials regarding "superiority" are conflicting, but suggest that both agents are effective. [50-53] Tazarotene plus mometasone was compared to calcipotriene monotherapy and was shown to be not significantly different in the percentage of patients achieving complete or almost complete clearance at any time during eight weeks of treatment.[54] Two other studies comparing calcipotriene to tazarotene showed similar results.[55-56]

Calcipotriene is formulated as a cream, ointment, solution and foam by itself and as an ointment and suspension when formulated with betamethasone. Calcitriol is only available topically as an ointment. Tazarotene is available as either a cream or gel. Tazarotene is currently the only agent with no generic available; although, calcipotriene foam (Sorilux®) is also only available as a branded medication.

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