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Joint AAD-NPF Guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures

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fJoint AAD-NPF Guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures

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The American Academy of Dermatology (AAD) strives to produce clinical guidelines that reflect the best available evidence supplemented with the judgment of expert clinicians. Significant efforts are taken to minimize the potential for conflicts of interest to influence guideline content. The management of conflict of interest for this guideline complies with the Council of Medical Specialty Societies' Code of Interactions with Companies. Funding of guideline production by medical or pharmaceutical entities is prohibited, full disclosure is obtained and evaluated for all guideline contributors throughout the guideline development process, and recusal is used to manage identified relationships. The AAD conflict of interest policy summary may be viewed at www.aad.org.

The information below represents the authors disclosed a relationship with industry during guideline development. Authors (listed alphabetically) with relevant conflicts with respect to this guideline are noted with an asterisk*. In accordance with the AAD policy, fewer than 51% of workgroup members had any relevant conflicts of interest.

Participation in one or more of the below-listed activities constitutes a relevant conflict:

- service as a member of a speaker bureau, consultant, advisory board, for pharmaceutical companies on the psoriasis disease state or psoriasis drugs in development or FDA-approved.
- sponsored research funding or investigator-initiated studies with partial/full funding from pharmaceutical companies on the psoriasis disease state or psoriasis drugs in development or FDA-approved.

Draft guideline recommendations were developed through a collaborative approach between conflicted and non-conflicted section leaders. Initial recommendations were presented to the full workgroup for finalization.

ABSTRACT

Psoriasis is a chronic, inflammatory, multisystem disease which affects up to 3.2% of the U.S population. This guideline addresses important clinical questions that arise in psoriasis management and care and provides recommendations based on the available evidence. The treatment of psoriasis with topical agents and with alternative medicine (AM) will be reviewed, emphasizing treatment recommendations and the role of dermatologists in monitoring and educating patients regarding benefits as well as risks that may be associated. This guideline will also address the severity assessment methods of psoriasis in adults.

Keywords: clinical guidelines for psoriasis; topical agents; severity assessment, alternative medicine (AM); dermatology; guidelines; psoriasis; skin disease

DISCLAIMER

Adherence to these guidelines will not ensure successful treatment in every situation. Furthermore, these guidelines should not be interpreted as setting a standard of care, nor should they be deemed either inclusive of all proper methods of care, or exclusive of other methods of care reasonably directed toward obtaining the same results. The ultimate judgment regarding the propriety of any specific therapy must be made by the physician and the patient in light of circumstances presented by the individual patient and the known variability and biological behavior of the disease. Furthermore, the treatment dosages used in clinical trials may not be effective in certain cases, and some patients may require shorter intervals between

doses and/or higher treatment doses of a particular treatment methodology. This guideline reflects the best available data at the time the guideline was prepared. The results of future studies may require revisions to the recommendations in this guideline to reflect new data.

ABBREVIATIONS USED

AAD: American Academy of Dermatology

AM: Alternative medicine

AV: Aloe Vera

BSA: body surface area

CYA: Cyclosporine

DLQI: Dermatology Life Quality Index

EPA: Eicosapentaenoic acid

FDA: the Food and Drug Administration

GFD: Gluten-free diet

HM: Herbal medicine

HPA: hypothalamic-pituitary-adrenal

LCD: Liquor carbonis detergens

NB-UVB: narrow band ultraviolet B

NPF: National Psoriasis Foundation

NAPSI: Nail Psoriasis Severity Index

PASI: Psoriasis Area Severity Index

PCB: Polychlorinated biphenyls

PGA: Physician's Global Assessment

PsA: Psoriatic arthritis

PSI: Psoriasis symptom inventory

QOL: Quality of life

RCT: Randomized controlled trial

SORT: Strength of Recommendation Taxonomy

UVA: ultraviolet A

UVB: ultraviolet B

WG: Work group

SCOPE

This guideline will cover the use of topical agents and alternative medicine (AM) in the treatment of psoriasis in adults as well as the assessment of disease severity; psoriasis in the pediatric population will be covered in a separate guideline section, "Joint AAD-NPF guidelines of care for the management and treatment of psoriasis in pediatric patients."[1]

METHOD

For a full description of the methodology used herein, please refer to the appendix section of the manuscript.

DEFINITION OF REVIEW

See Appendix for full definition statement.

INTRODUCTION

Psoriasis is a common inflammatory disease, affecting approximately 3.2% of the population.[2] While skin involvement is the most prominent manifestation of this disease,

recognition of psoriasis as a chronic, multisystem inflammatory disorder is imperative to optimize management and reduce comorbidities.

Topical medications are the most common agents used to treat mild to moderate psoriasis patients. They are frequently used as adjunctive therapies for patients on phototherapy, systemic, or biologic therapy. Alternative Medicine (AM) is not typically part of conventional medical care, it may have origins outside of usual Western practice and may be desired by and benefit a subset of patients.[3,4]

This section will review the assessment of psoriasis severity and the management and treatment of psoriasis with topical therapy and alternative medicine (AM) modalities in adult psoriasis patients.

Table 1. *Clinical Questions*

1. What are the efficacy, effectiveness and adverse events of the following therapies used as monotherapy and/or combination therapy to treat psoriasis in adults?
    a. Topical Steroids
    b. Topical Tacrolimus and Pimecrolimus
    c. Vitamin D analogues
    d. Tazarotene
    e. Moisturizers
    f. Salicylic Acid
    g. Anthralin
    h. Coal tar
    i. Biologic Agent Combination
    j. Non-Biologic Combination
        i. Methotrexate
        ii. Cyclosporine
        iii. Acitretin
        iv. Apremilast
2. What are the efficacy, effectiveness and adverse events of the following alternative medicines (AM) used for adult psoriasis?
    a. Traditional Chinese Medicine
    b. Herbal Therapies
        i. Aloe Vera
        ii. St. John's Wort

c. Diet/Dietary Supplements
    i. Fish oil
    ii. Vitamin D
    iii. Turmeric (Curcumin)
    iv. Zinc
    v. Gluten-Free Diet
d. Mind/Body
    i. Hypnosis
    ii. Stress Reduction/Meditation

3. What is the accuracy, clinical utility, and treatment parameters for using the following severity measures to measure psoriasis severity and response to treatment?
    a. Body Surface Area (BSA)
    b. Psoriasis Area and Severity Index (PASI)
    c. Physician Global Assessment (PGA)
    d. PGA x BSA
    e. Psoriasis Symptom Inventory (PSI)
    f. Dermatology of Life Quality Index (DLQI)
    g. Pruritus assessment

I. TOPICAL AGENTS

Topical Steroids

Efficacy

Topical corticosteroids, which provide high efficacy and good safety, play a key role in the treatment of psoriasis, especially for localized disease. Topical Steroids have anti-inflammatory, anti-proliferative, immunosuppressive, and vasoconstrictive effects. These effects are exerted via intracellular corticosteroid receptors, which regulate gene transcription, including several that code for pro-inflammatory mediators. Topical corticosteroids are classified into 7 categories based on their skin vasoconstrictive activity, ranging in strength from ultra-high (Class 1) to low (Class 6 and 7; see **Table 2**).[5,6]

Choosing a corticosteroid with appropriate potency plus the appropriate vehicle should be based on the disease severity, disease location, patient preference, as well as the age of the

patient. Lower potency corticosteroids should be used on the face, intertriginous areas, and areas that are susceptible to steroid atrophy (e.g. forearms) and other adverse effects. In adults, corticosteroids in classes 2 through 5 (moderate to high potency; see **Table 2**) are generally recommended as initial therapy. Areas with thick, chronic plaques often require treatment with Class 1 (ultra-high potency) corticosteroids. In numerous randomized controlled trials different potency topical corticosteroids were effective and safe at 2-4 weeks in the treatment of mild to severe plaque psoriasis.[7-9] Evidence on topical corticosteroids' efficacy from randomized controlled trials (RCT) varies due to the differences in study designs, patient populations, and endpoints, making it difficult to do an accurate statistical comparison of the majority of published studies.

For ultra-high potency (class 1) corticosteroids, the efficacy rates in several RCT vary from 58% to 92%.[7,8,10,11] In a double-blind, vehicle-controlled trial of 204 patients with moderate to severe psoriasis, after 2 weeks of treatment, the halobetasol propionate ointment (Class 1) group improved the Physician's Global Assessment (PGA) scores by 92% compared to 39% in vehicle-treated patients ($P<0.0003$).[7] An RCT of 279 patients with mild to moderate psoriasis found that after 2 weeks of treatment with clobetasol foam (class 1), 68% of patients achieved a Physician's Static Global Assessment (PSGA) score of 0 or 1 compared to 21% of patients treated with vehicle ($P<0.0001$).[8] Another double-blind, RCT of 81 patients used the IGA scale to assess patients with mild to moderate psoriasis and demonstrated that after 2 weeks of treatment with clobetasol foam (class 1), 58% of patients achieved moderate or marked improvement, or almost or completely clear psoriasis as compared to 15% in vehicle-treated patients ($P<0.0005$).[9]

For high potency (Class 2 and 3) corticosteroids, the efficacy rates in several RCTs vary from 68 to 74%. In a double blind-RCT of 35 patients with psoriasis treated with 0.25 % desoximetasone cream (Class 2) for 3 weeks, 68% of desoximetasone group compared to 23% of vehicle group achieved improvement in their mean overall evaluation scores (P<0.001).[12] Two RCTs with fluticasone propionate 0.005%, a class 3 corticosteroid, showed 68% to 69% of moderate to severe psoriasis patients in the treatment group achieved, good, excellent, or clear skin after 4 weeks, as compared with 29% to 30% in the vehicle group (P=0.00001).[13]

For moderate potency (Class 4 and 5) corticosteroids, the efficacy rates in several RCTs vary from 70% to 83%.[14,15] An RCT of 40 patients with non-scalp psoriasis revealed that 70% of patients treated with the betamethasone valerate foam 0.12% (Class 4) achieved greater than 50% improvement compared with 24% of patients in the placebo group after 12 weeks of treatment (P<0.001).[15] In an RCT of patients with moderate to severe scalp psoriasis, patients who were treated with fluocinolone acetonide 0.01% oil (Class 5 corticosteroid) had a higher proportion of patients achieving good or better improvement from baseline compared with the vehicle-treated group after 3 weeks of treatment (83 % vs 36%; p<0.001).[14] Additionally, an RCT showed that fluticasone propionate 0.05% cream (Class 5) was superior to hydrocortisone butyrate 0.1% cream (Class 7) in achieving clearance, excellent, or good treatment response after 3 weeks of treatment (79% vs 68%; p<0.05).[16]

Due to the inconsistent criteria in RCT design, comparisons between different corticosteroids and classes are complex. Nevertheless, a systematic review of topical corticosteroids for the treatment of psoriasis revealed that potent and super-potent topical corticosteroids were more efficacious than mild or moderate corticosteroids.[17]

Treatment of psoriasis in intertriginous areas, such as the groin or hair-bearing skin such as the scalp can be challenging due to the difficulty of applying a topical product to these areas based on the vehicle selection. Therefore, appropriate selection of the vehicle depending on hair density and individual hairstyles and preferences is essential for the efficacy of the treatment. Several RCTs and systematic reviews of scalp psoriasis treatment demonstrate the safety and efficacy of various potency topical steroids used for 3 to 12 weeks.[14,15,18] The duration of the therapy depends on factors such as the strength of topical steroids, the severity of the disease, anatomical location, and age of the patient. Similarly, a steroid-sparing agent can be considered to avoid adverse effects.

Additionally, intralesional steroids can be used for localized non-responding or very thick lesions on glabrous skin, scalp, nails, palms, and soles. Several studies and reports have shown that intralesional steroids can be effective for the treatment of psoriasis.[19-21] Triamcinolone acetonide in a dose up to 20mg/ml can be used every 3 – 4 weeks.[22] The injection volume varies pending lesional size and the area affected.

Table 2. Classification of topical corticosteroid [6,23,24*]

[*] Reprinted from Dermatology: 2-Volume Set, 4th Edition, Jean Bolognia, Julie Schafer, and Lorenzo Cerroni, Glucocorticosteroids, Page No. 2190, Copyright 2018, with permission from Elsevier.

WHO Potency Group	Classification	Topical Corticosteroid
Super-potent Ultra-high	Class 1	1. Augmented betamethasone dipropionate 0.05%[A,B] 2. Clobetasol propionate 0.05%[A,B,C,D,E,F,G,H,I] 3. Desoximetasone 0.25%[H] 4. Augmented Diflorasone diacetate 0.05%[A] 5. Fluocinonide 0.1%[C] 6. Flurandrenolide 4 mcg/cm^2 [J] 7. Halobetasol propionate 0.05%[A,C]
High	Class 2	1. Amcinonide 0.1%[A] 2. Betamethasone dipropionate 0.05%[A] 3. Augmented betamethasone dipropionate 0.05%[C,D] 4. Desoximetasone 0.25%[A,C] 5. Desoximetasone 0.05%[B] 6. Augmented Diflorasone diacetate 0.05%[C] 7. Diflorasone diacetate 0.05%[A] 8. Fluocinonide 0.05%[A,B,C,F] 9. Halcinonide 0.1%[A,C] 10. Mometasone furoate 0.1%[A] 11. Triamcinolone acetonide 0.5%[A]
	Class 3	1. Amcinonide 0.1%[C,D] 2. Betamethasone dipropionate 0.05%[C,K] 3. Betamethasone valerate 0.1%[A] 4. Betamethasone valerate 0.12%[L] 5. Diflorasone diacetate 0.05%[C] 6. Fluticasone propionate 0.005%[A] 7. Triamcinolone acetonide 0.1%[A] 8. Triamcinolone acetonide 0.5%[C]

[A] Ointment
[B] Gel
[C] Cream
[D] Lotion
[E] Foam
[F] Solution
[G] Scalp solution application, in some classifications class 2
[H] Spray
[I] Shampoo 0.05%
[J] Tape
[K] Lotion, Depending upon classification, class 3 or 5
[L] Foam, Depending upon classification, class 3 or 4

WHO Potency Group	Classification	Topical Corticosteroid
Moderate (Medium)	Class 4	1. Betamethasone valerate 0.12%[L] 2. Desoximetasone 0.05%[C] 3. Fluocinolone acetonide 0.025%[A] 4. Flurandrenolide 0.05%[A] 5. Hydrocortisone valerate 0.2%[A] 6. Mometasone furoate 0.1%[C,D] 7. Triamcinolone acetonide 0.1%[C,M] 8. Triamcinolone acetonide 0.2%[H]
	Class 5	1. Betamethasone dipropionate 0.05%[K] 2. Betamethasone valerate 0.1%[C,D] 3. Clocortolone pivalate 0.1%[C] 4. Fluocinolone acetonide 0.025%[C] 5. Fluocinolone acetonide 0.01%[N,O] 6. Fluticasone propionate 0.05%[C,D] 7. Flurandrenolide 0.05%[C,D] 8. Hydrocortisone butyrate 0.1%[A,C,D,F] 9. Hydrocortisone probutate 0.1%[C] 10. Hydrocortisone valerate 0.2%[C] 11. Prednicarbate 0.1%[A,C] 12. Triamcinolone acetonide 0.025%[A] 13. Triamcinolone acetonide 0.01%[D]
Low	Class 6	1. Alclometasone dipropionate 0.05%[A,C] 2. Betamethasone valerate 0.05%[D] 3. Desonide 0.05%[A,B,C,D,E] 4. Fluocinolone acetonide 0.01%[C,F] 5. Triamcinolone acetonide 0.025%[C,D]
	Class 7	1. Dexamethasone sodium phosphate 0.1%[C] 2. Hydrocortisone 0.5% - 2.5%[A,B,C,D,F] 3. Methylprednisolone acetate 0.25%[C]

[M] Kenalog® Ointment (Manufactured by APOTHECON, A Bristol-Myers Squibb Company; Princeton, NJ)
[N] Oil
[O] Shampoo

Risks/Harms and Benefits

The most common local skin side effects of topical steroid use include skin atrophy, striae, folliculitis, telangiectasia, and purpura.[25] Face and intertriginous areas as well as chronically treated areas especially forearms are at greatest risk to develop the above side effects. Topical corticosteroids may exacerbate acne, rosacea, perioral dermatitis, and tinea infections and may occasionally cause contact dermatitis. Rebound (i.e., when the disease recurs and is more severe than prior treatment) can occur from abrupt withdrawal of topical steroids, though the frequency and severity of this phenomenon are unknown. The daily use of ultra-high and high potency (class 1-3) corticosteroids for up to 4 weeks is generally safe with minimal risk of skin atrophy.[26]

Risk of hypothalamic pituitary adrenal (HPA) axis suppression from the use of topical corticosteroids for extensive plaque or scalp psoriasis has been reported to be low.[26] In a systematic review of 13 randomized studies, studies performed for up to 4 weeks found the percentage of patients with a reduction in morning cortisol level was 0% with halobetasol or fluocinonide, 0-48% with clobetasol propionate, and 0-18% with betamethasone dipropionate. Nevertheless, adrenocorticotropic hormone (ACTH) stimulation test, the gold standard for assessing HPA axis suppression, was always normal even when assessed after 6-12 months of topical steroid use.[26] Rare systemic side effects include Cushing syndrome and osteonecrosis of the femoral head.[27,28] Topical steroid-containing products should not be used for more than 12 weeks for nail disease, as there are isolated reports of bone atrophy with persistent use.[29,30] Increased intraocular pressure, glaucoma, and cataracts have been rarely reported with the use

of topical corticosteroids around the eye.[31,32] In rare cases, type 2 diabetes has been reported with topical corticosteroid use.[33]

Despite the safety data[26], caution is advised, as the greatest risk for systemic side effects occurs when ultra-high or high potency steroids are used over a large surface (>20% BSA) or under occlusion for a prolonged period (>4 weeks). Clinicians should consider limiting the use of Class 1 corticosteroids to no more than twice daily for up to 4 weeks when possible.[34] In the event of a flare, repeated courses of class 1 corticosteroid can be administered. Longer durations of Class 1 steroid therapy for psoriasis of the palms and soles are acceptable with close attention to the development of potential side effects. Gradual reduction in the frequency of usage following clinical improvement is recommended, but the exact details of this tapering are not well established. Topical corticosteroids can be tapered off by reducing use to every other day, then eventually two times a week, and finally discontinuation if psoriasis is well controlled and stable during the whole process. To minimize the side effects of topical corticosteroids, transitioning to lower potency agents after improvement, using intermittent therapy, and combining treatment with non-steroidal agents can also be considered.

Topical corticosteroids are safe during pregnancy when low cumulative doses (less than 60 gram per week) are used (expert consensus). In rare cases, low fetal birth weight has been reported with prolonged potent topical corticosteroid use during pregnancy.[38] Further, there is a single case report of a nursing mother who applied a potent topical steroid on the nipple and the infant developed hypertension.[37] Therefore, the use of a super potent corticosteroid in the nipple and the areola area should be avoided in nursing mothers.[35,36]

General comments

Since psoriasis generally recurs after discontinuation of topical corticosteroid treatment, it is important to consider using steroid-sparing agents that have been developed to supplement and reduce over-reliance on topical steroids as monotherapy, decreasing the risk of steroid side effects.[26] Agents such as vitamin D analogues, topical retinoids, and calcineurin inhibitors can be used as a maintenance treatment. For example, a therapeutic regime for mild psoriasis flares could include 2-4 weeks of treatment with a topical steroid twice daily, followed by maintenance with a steroid-sparing agent twice daily (BID) on weekdays, and a steroid agent BID on weekends.[39] Treatment as discussed above can be re-instituted when a new flare occurs. "Proactive treatment" is another strategy for optimal topical management of psoriasis during maintenance that is helpful. Proactive treatment refers to topical treatment of areas that are clinically quiescent but are usually involved in recurrence. It typically involves twice-weekly treatment of these clinically quiescent areas to reduce the frequency of flares.[40,41] Proactive treatment can be implemented with any of the topical agents discussed in these guidelines.

Tachyphylaxis is defined as the loss of effectiveness of topical steroids with continued use. Tachyphylaxis may compromise the effectiveness in certain patients when used for an extended period > 12 weeks. It is controversial whether tachyphylaxis represents a true loss of effectiveness of the medication or a loss of adherence on the part of patients. Current suggestions are based on extrapolation from animal studies, and further research into this subject is needed.[39,42-44]

Table 3. *Recommendations and strength of recommendation for topical steroids*

Reference number	Recommendations	Strength of recommendation

1.1	The use of class 1, class 2, and class 3-5 topical steroids for up to 4 weeks is recommended for the treatment of plaque psoriasis not involving intertriginous areas	A
1.2	The use of class 1-7 topical steroids for a minimum of up to 4 weeks is recommended as initial and maintenance treatment of scalp psoriasis	A
1.3	The use of topical corticosteroids for > 12 weeks can be considered if done under the careful supervision of a physician	C

Table 4. *Level of evidence for topical Steroids*

Recommendation	Reference Number	Level of Evidence	Studies
Topical steroid for plaque psoriasis not involving intertriginous areas	1.1	I	7-9,11,13,45-47
Topical steroid for scalp psoriasis	1.2	I	14,15,18
Long-term use of topical corticosteroid	1.3	III	Expert Opinion

Calcineurin inhibitors

Efficacy

Topical calcineurin inhibitors bind to calcineurin, blocking its phosphorylation and thus, inhibiting T cell activation and the synthesis of several pro-inflammatory cytokines that play a critical role in the pathogenesis of psoriasis. While not FDA approved for psoriasis, the topical calcineurin inhibitors Tacrolimus and Pimecrolimus are often employed in the treatment of psoriasis. They are especially helpful on thinner skin such as facial and intertriginous areas and used as steroid-sparing agents for prolonged use (> 4 weeks). The majority of the data regarding these medications are derived from their extensive use in atopic dermatitis.

Several RCTs support the use of Pimecrolimus for the treatment of intertriginous psoriasis.[55,56] In a double-blind RCT of 57 patients with intertriginous psoriasis, after 8 weeks of twice-daily treatment, 71% of the patients in the Pimecrolimus 0.1% cream group were clear or

almost clear as compared with 21% of patients in the placebo group [treatment difference in target area score= -1.810; 95% CI -2.801 to -0.819].[56] There are also several RCTs that support the use of Tacrolimus for the treatment of facial and intertriginous psoriasis.[57] In a double-blind RCT of 167 patients with facial and intertriginous psoriasis, after 8 weeks of therapy, 65% of patients in the Tacrolimus 0.1% ointment group were clear or almost clear as compared with 31% of patients in the placebo group.[58]

The off-label combination of Tacrolimus and 6% salicylic acid for 12 weeks may be used for the treatment of plaque psoriasis.[59]

Risks/Harms and Benefits

Based on studies from atopic dermatitis, both Tacrolimus and Pimecrolimus can cause burning and pruritus.[60-63] These adverse events generally improve with continued use and can be mitigated by avoiding application to moist skin.[60,61]

In 2005 the FDA issued a boxed warning citing concerns that chronic, intermittent use of Pimecrolimus or Tacrolimus could lead to an increased incidence of lymphoma. This warning was due to a theoretical increased risk of lymphoma with the systemic use of these agents based upon animal data, isolated case reports, and the mechanism of action of these drugs. Although both agents carry a boxed warning related to the potential risk for malignancy (e.g. skin and lymphoma), there is no evidence showing an increased risk of malignancy with the topical use of either agent.[60,61,64-66] A common side effect of calcineurin inhibitors includes flushing with the ingestion of alcohol.[60,61]

The effects in humans of Tacrolimus and Pimecrolimus on the fetus are unknown; if they are used during pregnancy, they should, therefore, be used cautiously. Breastfeeding mothers

should avoid use on the nipple but can use them on other areas, as maternal systemic absorption is minimal.[60,61,67] Additionally, no signs of reduced fertility were found in males and females using Tacrolimus.[61] Similarly, in animal studies, no signs of reduced fertility were associated with Pimecrolimus.[60]

Contraindication

There are no specific contraindications, but much of the data (except that given above for facial and intertriginous psoriasis) regarding these medications are derived from their extensive use in atopic dermatitis.

Table 5. *Recommendations and strength of recommendation for topical Pimecrolimus and Tacrolimus*

Reference number	Recommendations	Strength of recommendation
2.1	The off-label use of 0.1% Tacrolimus for psoriasis involving the face as well as inverse psoriasis for up to 8 weeks can be considered	B
2.2	The off-label use of Pimecrolimus for inverse psoriasis for 4-8 weeks is recommended	B
2.3	Long term use of Tacrolimus or Pimecrolimus can be considered for inverse psoriasis treatment as off-label use	C
2.4	The off-label combination of Tacrolimus and 6% salicylic acid for 12 weeks may be used for the treatment of plaque psoriasis	B

Table 6*. Topical Pimecrolimus and Tacrolimus level of evidence*

Recommendation	Reference Number	Level of Evidence	Studies
Use of 0.1% Tacrolimus for psoriasis involving the face/inverse psoriasis	2.1	I	[57,58]
Use of Pimecrolimus for inverse psoriasis	2.2	I	[55,56]
Long term use of Tacrolimus or Pimecrolimus for inverse psoriasis	2.3	III	[68]

Combination of Tacrolimus and 6% salicylic acid for plaque psoriasis	2.4	II	[59]

Vitamin D analogues

Efficacy

Vitamin D analogues exert their effect in psoriasis by binding to vitamin D receptors, which inhibit keratinocyte proliferation and enhances keratinocyte differentiation. Calcipotriene (also known as calcipotriol) and calcitriol are the two commonly used synthetic vitamin D analogues. While calcipotriene is available in several formulations in the US, topical calcitriol is only available as an ointment. Tacalcitol and maxacalcitol are vitamin D analogues available worldwide, but not currently in the US. Additionally, calcipotriene and tacalcitol are available in combination with topical steroids. Several studies have shown that 4-8 weeks treatment of calcipotriene, calcitriol, tacalcitol, and maxacalcitol is safe and efficacious for treating mild to moderate psoriasis.[69-71] Two double-blind RCT compared calcipotriene foam to the vehicle for the treatment of plaque psoriasis. In the first study, 14% of subjects in the calcipotriene foam group versus 7% of subjects in the vehicle foam group achieved treatment success after 8 weeks (p=0.058). In the second study, treatment success and primary endpoint, defined as achieving an Investigator's Static Global Assessment (ISGA) score of 0 or 1 (clear or almost clear), was achieved by more subjects in the calcipotriene foam group (27% vs 16%; p=0.016).[72] A 6-week double-blind RCT in 258 plaque psoriasis patients showed that calcitriol ointment had comparable efficacy, defined as a mean reduction of PASI, to betamethasone dipropionate 0.05% ointment (10.6% and 9.67% respectively).[10] During the post-treatment follow-up 48% of patients who took calcitriol and 25% of patients who took betamethasone dipropionate remained in remission (P<0.01). Treatment with calcipotriene foam for 8 weeks

and calcipotriene plus betamethasone dipropionate gel for 4-12 weeks compared to placebo was safe and effective for the treatment of mild to moderate scalp psoriasis.[73,74]

An 8-week double-blind RCT with 363 psoriasis patients used the investigator static global assessment (ISGA) to measure its primary outcome. After 8 weeks, calcipotriene foam (40.9%) was more effective in achieving an ISGA score of 0 (clear) or 1 (almost clear) compared to vehicle (24.2%) for the treatment of scalp psoriasis (P<0.001).[75] The efficacy of vitamin D analogues was noted at 8 weeks, but not at 4 weeks. This can be considered and addressed with patients when planning appropriate topical treatment. The use of calcipotriene or tacalcitol ointment combined with hydrocortisone is efficacious for the treatment of facial psoriasis.[76] Topical calcipotriene has displayed greater efficacy than either 6% coal tar or salicylic acid, but less efficacy than liquor carbonis detergens (LCD) 15% solution.[77,78] An 8-week double-blind RCT (N=409) with 4 treatment arms compared calcipotriene 25 mcg/g, calcipotriene 25 mcg/g plus hydrocortisone 10mg/g, calcipotriene 50 mcg/g, calcipotriene 50mcg/g plus hydrocortisone 10mg/g.[79] All treatments are equally effective on the body, but the treatments containing hydrocortisone were more effective on the face as determined by a score of 0 or 1 in the IGA of the face (OR=2.01; 95% CI 1.33 to 3.05, p=0.001).[79]

The use of combination treatments with Vitamin D analogues and potent topical steroids from 3 to 52 weeks is more effective than either agent alone for the treatment of psoriasis.[80-91] A systematic review of RCTs concluded that when given for 3-8 weeks,ultra potent or potent steroid treatments outperform calcipotriene. The outcome measures assessed in the review included IGA, PASI, and PGA which were translated to a 6-point improvement scale. Nevertheless, calcipotriene combined with potent betamethasone dipropionate was slightly

more efficacious than betamethasone as a monotherapy.[92] In a 52-week study with 828 patients, 69% to 74% of patients in the group treated with calcipotriene 0.005% plus betamethasone 0.064% once or twice daily achieved clear or almost clear status compared to 27% of the patients treated with vehicle control ($p< 0.001$). No serious adverse events, including striae or HPA axis suppression, were observed over the 52-week treatment period with calcipotriene 0.005% and betamethasone 0.064%.[88] There is evidence supporting the application of vitamin D analogues twice daily on weekdays in conjunction with high potency topical steroids twice daily on weekends.[39] An open-label study in 70 patients showed treatment with calcipotriene ointment on weekdays and clobetasol spray-on weekends applied twice daily for four weeks is an effective treatment regimen for moderate plaque psoriasis.[39] Additionally, the application of morning high potency topical steroids and evening topical vitamin D analogues is an effective combination regimen for the treatment of psoriasis.[93] In an open-label study, 68 patients applied an AM/PM regimen of clobetasol propionate spray 0.05% and calcipotriene ointment 3 micrograms/gram. At 4 weeks, 85.5% of patients were clear, almost clear, or had mild involvement.[93]

Risks/Harms and Benefits

Vitamin D analogues are considered safe for the treatment of plaque psoriasis. No clinical or experimental evidence has been found relating to tachyphylaxis with topical vitamin D analogue usage in psoriasis. Other local side effects can affect up to 35% of patients and include burning, pruritus, edema, peeling, dryness, and erythema. They may occur both on lesional and perilesional skin. With continued treatment, these side effects usually subside or disappear. Systemic side effects due to topical vitamin D analogues include hypercalcemia and

parathyroid hormone suppression. These effects are quite rare unless more than 30% BSA is treated, the recommended dose is exceeded, or the patient has an underlying renal disease or impaired calcium metabolism. When using calcipotriene, applications of over 100 grams per week should be avoided to minimize this risk.[94] Calcipotriene over 52 weeks was well tolerated in an open-label study of 132 patients . A total of 3.1% of patients experienced mild hypercalcemia that did not correlate with the length of treatment or pretreatment BSA.[20] Vitamin D analogues may be used during pregnancy and lactation if the benefit outweighs the risk. The use of vitamin D combination products containing corticosteroids on over 15% BSA once daily rarely induces adrenal suppression.[95]

General Comments

Ultraviolet A radiation can decrease the concentration of calcipotriene on the skin. Conversely, thick layers of calcipotriene can block UVB thereby increasing the minimal erythema dose (MED).[96] Vitamin D analogues can be used in conjunction with phototherapy but should be applied subsequent to phototherapy treatment to avoid inactivation by ultraviolet A and blocking B radiation (UVA/UVB).[97] Combining separate vitamin D and corticosteroid preparations into specific easy-to-follow regimens can be used to reduce both the side effects of topical steroids and reduce the cost for some patients, as discussed above in the topical steroid section. Additionally, the simultaneous use of salicylic acid with calcipotriene should be avoided as the acid pH of salicylic acid will inactivate calcipotriene and reduce its effectiveness.

Topical vitamin D analogues combined with betamethasone dipropionate can be used for the treatment of nail psoriasis to reduce nail thickness, hyperkeratosis, onycholysis, and pain.[30] These agents have limitations in treating severe nail disease due to poor penetration,

particularly of the nail matrix.[98] Topical maxcalcitol (not available in the US) ointment can be considered as initial treatment for palmoplantar psoriasis including palmoplantar pustulosis.[99,100]

Other combination treatments

Calcipotriene ointment combined with topical Tacrolimus is more efficacious than Tacrolimus alone.[101] Combination products with calcipotriene and topical nicotinamide are effective for the treatment of mild to moderate psoriasis.[102]

Table 7. *Recommendations and strength of recommendation for Vitamin D analogues*

Reference number	Recommendations	Strength of recommendation
3.1	The long-term use of topical vitamin D analogues (up to 52 weeks) including calcipotriene/calcipotriene, calcitriol, tacalcitol, and maxacalcitol is recommended for the treatment of mild to moderate psoriasis	A
3.2	Use of calcipotriene foam and calcipotriene plus betamethasone dipropionate gel is recommended for 4-12 weeks for the treatment of mild to moderate scalp psoriasis	A
3.3	Topical tacalcitol ointment or calcipotriene combined with hydrocortisone for 8 weeks can be used for the treatment of facial psoriasis	B
3.4	Use of combination treatments with vitamin D analogues and potent Class II and Class III topical steroids up to 52 weeks is recommended for the treatment of psoriasis	A
3.5	Use of combination products with calcipotriol and corticosteroids is recommended for the treatment of psoriasis	A
3.6	The application of vitamin D analogues twice daily on weekdays in conjunction with high potency topical steroids twice daily on weekends can be considered for maintenance treatment for psoriasis	B
3.7	The application of morning high potency topical steroids and evening topical vitamin D analogues is an effective treatment regimen that can be considered for the treatment of psoriasis	B

388 ***Table 8****. Level of evidence for vitamin D analogues*

Recommendation	Reference Number	Level of Evidence	Studies
Topical vitamin D analogues therapy	3.1	I-II	10,18,20,72,103
Treatment with calcipotriene foam and calcipotriene plus betamethasone dipropionate gel for scalp psoriasis	3.2	I	73-75,104
Topical tacalcitol ointment or calcipotriene combined with hydrocortisone for facial psoriasis	3.3	I-II	76,79
Combination treatments with vitamin D analogues and potent topical steroids for psoriasis	3.4	I-II	80-87,92,105
Combination products with calcipotriene and corticosteroids for psoriasis	3.5	I-III	89-91,106-108
Application of vitamin D analogues twice daily on weekdays in conjunction with high potency topical steroids twice daily on weekends	3.6	II	39
Morning high potency topical steroids and evening topical vitamin D analogues	3.7	II	93

389 **Tazarotene**

390 ***Efficacy***

391 Tazarotene is a topical retinoid available for the treatment of psoriasis since 1997. It
392 exerts its therapeutic effects by acting on keratinocyte differentiation and proliferation, and by
393 downregulating the expression of pro-inflammatory genes. The use of topical tazarotene for 8-
394 12 weeks is recommended for the treatment of mild to moderate psoriasis with several studies
395 demonstrating its efficacy.[109-112] In two RCT of 1,303 patients with plaque psoriasis, 40% and
396 51% of patients treated with tazarotene (0.1% cream and 0.05% cream, respectively) compared
397 to 25% of patients treated with the vehicle once daily for 12 weeks achieved treatment success,
398 defined as overall lesional assessment of none, minimal, or mild psoriasis activity (P for trend=
399 0.04).[113] A 12-week RCT showed that the efficacy of tazarotene 0.1% gel for the treatment of
400 plaque psoriasis was comparable to fluocinonide cream. The efficacy was assessed by

measuring plaque elevation, scaling, and erythema (grading each from 0 to 4) of target lesions at baseline and at each follow-up visit. Treatment success was defined as 50-74% improvement.[110]

An RCT showed that the combination of tazarotene 0.1% gel plus clobetasol propionate 0.05% ointment was more effective than tazarotene gel alone in maintaining clearance after 20 weeks.[51] Tazarotene can also be combined with phototherapy. An RCT showed tazarotene plus narrowband ultraviolet B (NB-UVB) therapy improved the efficacy of phototherapy and decreased the amount of UV radiation needed to achieve 50% or better improvement from baseline using the 6-point global improvement scale.[114]

A double-blind RCT compared the efficacy of tazarotene 0.1% cream with clobetasol 0.05% cream both under occlusion for 12 weeks for nail psoriasis. The efficacy was assessed using the Nail Psoriasis Severity Index (NAPSI). At 12 weeks, both groups showed significant improvement in NAPSI with respect to onycholysis, pitting, hyperkeratosis, and oil spots (salmon patches). Additionally, the difference in efficacy between both groups was not statistically significant.[115] A smaller double-blind placebo-controlled clinical trial with 31 patients assessed the efficacy of tazarotene for the treatment of nail psoriasis. After 24 weeks of treatment, tazarotene 0.1% gel showed a significantly greater reduction of onycholysis (in occluded and non-occluded nails) and pitting (in occluded nails) compared to placebo ($p \leq 0.05$).[116]

Risks/Harms and Benefits

Potential side effects include erythema, burning, and pruritus and are more prominent at higher concentrations.[117] Avoid the application of formulation to uninvolved skin to minimize

irritation. These side effects can be reduced by using a cream formulation or lower concentration formulation, combining tazarotene with moisturizers, applying it on alternate days or short-contact (30 to 60 minutes) treatment, and combining it with topical corticosteroids.[54] The combination of tazarotene with halobetasol is beneficial because it reduces the irritation caused by tazarotene. Additionally, the combination reduces the amount of topical corticosteroids needed, thereby limiting atrophy produced by halobetasol.[118] Tazarotene should be avoided in pregnant women. In women of childbearing age, a negative pregnancy test should be obtained 2 weeks prior to starting tazarotene according to the package insert.[54] Women of childbearing age should be counseled to discontinue tazarotene if they become pregnant. No human data are available on excretion in human milk. No signs of fertility reduction based on animal studies have been reported.[54]

Contraindication

Tazarotene should not be used in pregnant women.

Topical Steroids & Tazarotene

The use of mid potency or high potency topical steroid in combination with tazarotene for 8-16 weeks is recommended for the treatment of mild to moderate psoriasis.[50] There may be a synergistic effect when topical Steroids are used along with tazarotene, and this combination also increases the duration of treatment effect as well as the time of remission.[51,52] A multicenter RCT of 300 patients with stable plaque psoriasis with ≤20% body surface area involved treated with tazarotene 0.1% gel once daily either alone or combined with low, medium or high potency topical corticosteroids demonstrated the combination of tazarotene with medium potency or high potency topical corticosteroid increased efficacy while

reducing local adverse events.[53] For details related to the treatment of psoriasis with tazarotene monotherapy as well as potential risk/harm refer to the respective section below. Tazarotene is contraindicated during pregnancy and should be discontinued if pregnancy is recognized.[54]

General Comments

Topical tazarotene can be particularly helpful for palmar-plantar psoriasis and nail psoriasis. Topical tazarotene studies have similar efficacy to fluocinonide cream, crude coal tar 5% ointment, and calcipotriene 0.005% ointment.[110-112] Topical steroids can be added to topical tazarotene to increase efficacy.

Table 9. *Recommendations and strength of recommendation for topical tazarotene*

Reference number	Recommendations	Strength of recommendation
4.1	Topical tazarotene can be used for the treatment of mild to moderate psoriasis	B
4.2	Topical tazarotene can be used for the treatment of nail psoriasis	B
4.3	The combination of topical tazarotene and NB-UVB has been shown to be effective and allow a reduction in total usage of NB-UVB	B
4.4	The use of mid-potency or high potency topical steroid in combination with tazarotene for 8-16 weeks is more effective than monotherapy with tazarotene and is recommended for the treatment of mild to moderate psoriasis	A
4.5	The use of topical steroids along with tazarotene is recommended to decrease the duration of treatment as well as increase the length of remission	A

Table 10. Topical tazarotene level of evidence

Recommendation	Reference Number	Level of Evidence	Studies
Tazarotene for mild to moderate psoriasis	4.1	I-III	51,109-113
Tazarotene for nail psoriasis	4.2	I-II	50,119,120

Tazarotene and NB-UVB combination	4.3	II	[114]
Monotherapy (tazarotene) vs combination with mid to high potency topical steroid for psoriasis	4.4	I	[50,53]
Synergistic effect of combination therapy	4.5	I	[51,52]

Moisturizers

Efficacy

Non-medicated moisturizers are available in several formulations (i.e., creams, ointments, lotions, gels, etc). They can be used as part of a general treatment regimen for psoriatic patients to help reduce itching and desquamation. Emollients, one type of moisturizer, exert their action by retaining moisture in the stratum corneum. An RCT showed the combination of mometasone plus emollient improved the area of palmoplantar skin affected, desquamation, and symptoms compared to mometasone alone after 4 weeks of treatment.[121] Emollients have no known contraindications unless there is hypersensitivity to their ingredients.

Risks/Harms and Benefits

There is a small risk of contact dermatitis with some emollients. Emollients, like any other topical agents, may be inconvenient to apply on a regular basis for patients with a large body surface area of involvement. Moisturizers are considered safe during pregnancy and lactation.

General comments

Moisturizers can be safely applied several times a day.

Table 11. Recommendations and strength of recommendation for emollient

Reference number	Recommendations	Strength of recommendation
5.1	The use of an emollient in conjunction with topical	B

	corticosteroids for 4 to 8 weeks can be used to help reduce itching, desquamation, and total body surface area and prevent quick relapse of psoriasis when topical corticosteroids are discontinued	

Table 12. Level of evidence for emollient

Recommendation	Reference Number	Level of Evidence	Studies
Emollients in conjunction with topical corticosteroid therapy	5.1	II	[121,122]

Salicylic Acid

Efficacy

Salicylic acid is used as a topical keratolytic agent in the treatment of psoriasis. Its mechanism of action is believed to involve the reduction of the binding between keratinocytes; it minimizes scaling and softens psoriatic plaques.[123] Topical salicylic acid use for 8-16 weeks is recommended for the treatment of mild to moderate psoriasis. Salicylic acid is effective for the treatment of psoriasis, alone or combined with other topical therapies, including corticosteroids and topical immunomodulators.[59,77,124,125] The improvements in efficacy seen with combination therapy compared with steroid alone is likely due to the increased skin penetration caused by salicylic acid. An open-label study of 10 patients assessed the efficacy of 6% salicylic acid in an ammonium lactate vehicle for the treatment of scalp psoriasis. After 4 weeks of monotherapy, the mean Psoriasis Scalp Severity Index (PSSI) decreased from 15 to 3.[125] An RCT with 408 psoriasis patients revealed that mometasone 0.1% with salicylic acid was superior to mometasone 0.1% ointment after 21 days of twice-daily use for plaques on upper and lower extremities.[48] Additionally, the combination of Tacrolimus with 6% salicylic acid was more effective than salicylic acid plus vehicle.[59]

Risks/Harms and Benefits

Systemic absorption and increased risk for salicylate toxicity are higher in patients with renal disease and patients with hepatic disease when treating large body surface areas (>20%); therefore, its use should be avoided or used with caution in these groups. Topical salicylic acid should not be applied before ultraviolet B (UVB) phototherapy as it reduces its efficacy.[126,127] There are inadequate human data available for the use of salicylic acid during pregnancy/lactation.

Topical Steroids & salicylic acid

The combination of salicylic acid with topical corticosteroids can be used for the treatment of moderate to severe psoriasis (BSA ≤ 20%) as well as palmar-plantar psoriasis. Two randomized multicenter studies demonstrated the addition of salicylic acid to mometasone furoate is safe and more effective than mometasone alone.[48,49] High potency topical corticosteroids can be used in combination with salicylic acid but caution must be used to ensure only small quantities of the high strength corticosteroid are used to reduce the potential risk of systemic absorption of the Steroid.

Table 13. *Recommendation and strength of recommendation for salicylic acid*

Reference number	Recommendations	Strength of recommendation
6.1	Topical salicylic acid can be used for 8-16 weeks for the treatment of mild to moderate psoriasis	B
6.2	The combination of salicylic acid with topical corticosteroids can be used for the treatment of moderate to severe psoriasis (BSA ≦ 20%)	B

Table 14. *Level of evidence for salicylic acid*

Recommendation	Reference Number	Level of Evidence	Studies

Topical salicylic acid for mild to moderate psoriasis	6.1	I-II	48,59,77,124,125
Salicylic acid plus topical corticosteroid for psoriasis	6.2	I	48,49

Anthralin (dithranol)

Efficacy

Anthralin is a polycyclic aromatic hydrocarbon derivative. The exact mechanism of action of anthralin is not fully understood, although it is thought to be mediated by preventing T-lymphocyte activation and promoting keratinocyte differentiation.[128]

Topical anthralin is effective in the treatment of psoriasis.[129-132] 8-12 weeks use of topical anthralin is recommended for the treatment of mild to moderate psoriasis starting at 0.1% concentration with increasing concentration over time as tolerated. Short contact (up to 2 hours per once daily application) anthralin therapy (SCAT) is recommended to limit side effects. Two small RCTs with 12 and 25 psoriasis patients assessed the efficacy of an aqueous gel formulation of anthralin and an anthralin ointment, respectively. After 4 weeks of twice-daily 1-minute treatments, anthralin demonstrated significantly better results than placebo and similar efficacy to topical calcipotriene.[129,130] An RCT of 106 patients comparing calcipotriene and short contact dithranol showed no statistically significant difference in the quality of life over 12 weeks between the two treatments.[131]

Combination treatment of anthralin with excimer laser showed better results than anthralin alone and similar results to the combination of 308 nm laser plus topical calcipotrienel.[132]

Risks/Harms and Benefits

Side effects include perilesional erythema, burning, and mild-to-severe staining of the skin. These are improved by using the short contact application method (up to 2 hours). Application should be avoided to the face or other highly visible areas. There is no evidence of any topical or systemic toxicities related to prolonged anthralin use. There are no data available on human milk excretion.

Precaution

Anthralin can temporarily stain the skin and application should be avoided to the face or other highly visible areas. The use of anthralin on the face and flexures should be avoided.

Table 15. *Recommendation and strength of recommendation for topical anthralin*

Reference number	Recommendation	Strength of recommendation
7.1	Topical anthralin for 8-12 weeks can be used for the treatment of mild to moderate psoriasis. Short contact (up to 2 hours per day) anthralin is recommended to limit side effects	B

Table 16. *Topical anthralin level of evidence*

Recommendation	Reference Number	Level of Evidence	Studies
Topical anthralin for mild to moderate psoriasis	7.1	I-III	129,131-133

Coal Tar/liquor carbonis detergens (LCD)

Efficacy

Coal tar, a distillation product from coal, is a heterogeneous mixture of thousands of chemical compounds. Its composition differs between preparations. It has been used for the treatment of psoriasis for over a century. The polyaromatic hydrocarbons bind to the Aryl hydrocarbon receptor and tar is known to decrease keratinocyte proliferation by suppressing

DNA synthesis. It also suppresses inflammation and may affect immunological function. Several clinical trials and a systematic review have shown the efficacy of coal tar in the treatment of psoriasis.[77,78,111,134-139] The use of coal tar preparations is recommended for the treatment of mild to moderate psoriasis. An RCT compared 1% coal tar lotion with 5% coal tar extract among 324 patients with mild to moderate psoriasis. The improvement in Total Sign Score (TSS) score was better in patients treated with 1% lotion than with 5% extract (-10.6%; 95% CI -20.6% to -0.5%; P=0.04).[134] Another RCT of 60 patients compared LCD 15% solution and calcipotriene 0.005% cream. The LCD group had greater mean reductions in PASI scores than calcipotriene group at 12 weeks (58% vs 37%; p<0.05).[78] Coal tar can also be combined with NB-UVB resulting in reduction of the time to clearance and improved therapeutic outcome compared to NB-UVB alone.[138,139] An example of that is Goeckerman therapy, which consists of the application of coal tar and exposure to narrowband ultraviolet B (NB-UVB) light.

Risks/Harms and Benefits

The risks of coal tar application include local irritation, folliculitis, contact dermatitis, and phototoxicity. Possible carcinogenicity has remained controversial, but not proven. Dermatologic studies on topical preparations have not revealed an increased risk, but animal and occupational studies document carcinogenicity with prolonged exposures over many years.[140,141] A retrospective analysis of human use of coal tar preparations during pregnancy has not shown any adverse effects on the fetus, although in animal studies large doses have been observed to increase the risk of cleft palates, small lungs, and perinatal mortality.[142,143] Thus, it may be advisable to avoid the use of coal tar preparations during pregnancy and lactation.[36,144] Coal tar preparations have frequently been used in conjunction with phototherapy. While the

application of coal tar one day prior to phototherapy may be helpful, the application just prior to phototherapy can cause tar pigmentation. Refer to the Joint AAD-NPF Guideline on Phototherapy Guideline in reference to Goeckerman therapy.[97]

Precaution

Coal tar products can stain clothes and tar odor is present in most preparations, thus reducing patient adherence.

Table 17. *Recommendations and strength of recommendation for coal tar*

Reference number	Recommendation	Strength of recommendation
8.1	Coal tar preparations are recommended for the treatment of mild to moderate psoriasis	A
8.2	*According to the joint AAD-NPF phototherapy guideline*[97], there is sufficient evidence to recommend the use of Goeckerman therapy for the treatment of psoriasis	B

Table 18. *Level of evidence for coal tar*

Recommendation	Recommendation Number	Level of Evidence	Studies
Use of coal tar for psoriasis	8.1	I-II	77,78,111,134-139
Goeckerman therapy for psoriasis	8.2	II-III	145,146

Topical agents in combination with systemic therapies

Topical agents in combination with biologics

All topical steroids can be used with biologic agents for the treatment of psoriasis. The addition of an ultra-high potency (class 1) topical corticosteroid to standard dose etanercept lead to improved efficacy without any increased safety concerns.[147] This advantageous effect of combination therapy at 12 weeks disappeared by 24 weeks.[147] The addition of calcipotriene/betamethasone to standard dose adalimumab resulted in higher efficacy than

adalimumab monotherapy at 4 weeks, but at 16 weeks, there was no difference in efficacy between the two groups.[148]

Table 19. *Recommendations and strength of recommendation for the combination of topical agents with biologics*

Recommendation Number	Recommendation	Strength of Recommendation
9.1	The addition of an ultra-high potency (Class 1) topical corticosteroid to standard dose etanercept for 12 weeks is recommended for the treatment of moderate to severe psoriasis	A
9.2	The addition of calcipotriene/betamethasone to standard dose adalimumab for 16 weeks is recommended for the treatment of moderate to severe psoriasis to accelerate clearance of psoriatic plaques.	B
9.3	All topical steroids can be used in combination with any biologics for the treatment of moderate to severe psoriasis	C

Table 20. *Level of evidence for the combination of topical agents with biologics*

Recommendation	Recommendation Number	Level of evidence	Studies
Addition of Class 1 topical corticosteroid to standard dose etanercept for psoriasis	9.1	I	[147]
Addition of calcipotriene/betamethasone to standard dose adalimumab for psoriasis	9.2	I	Expert opinion
Topical corticosteroid with biologic for treatment of psoriasis	9.3	III	Expert Opinion

Topical agents in combination with non-biologic therapies

Topical calcipotriene & methotrexate

The addition of topical calcipotriene to standard dose methotrexate leads to lower cumulative doses of methotrexate and increased time to relapse following its discontinuation.[149] A multicenter RCT (vehicle-controlled) demonstrated that when

589 calcipotriene was added to weekly methotrexate, calcipotriene decreased the necessary dosing

590 of methotrexate from 9.9 to 6.5 mg per week (P=0.002).[149]

591 **Table 21**. *Recommendation and strength of recommendation for the combination of topical*

592 *calcipotriene and methotrexate*

Recommendation Number	Recommendation	Strength of recommendation
10.1	The addition of topical calcipotriene to standard dose methotrexate therapy is recommended for the treatment of moderate to severe psoriasis. It may lead to lower cumulative doses of methotrexate and increased time to relapse following methotrexate discontinuation.	A

593 **Table 22**. *Level of evidence for the combination of topical calcipotriene and methotrexate*

Recommendation	Recommendation Number	Level of Evidence	Studies
Calcipotriene and methotrexate for psoriasis	10.1	I	[149]

594 ***Topical agents & cyclosporine***

595 The addition of calcipotriene/betamethasone dipropionate ointment to low dose

596 cyclosporine (2 mg/kg/day) enhances the clinical response of cyclosporine. An open-label RCT

597 of patients with moderate to severe psoriasis demonstrated that 30 patients given 2 mg/kg/day

598 cyclosporine along with calcipotriene/betamethasone had a significantlyhigher PASI 75 at 8

599 weeks of treatment than 30 patients treated with 2 mg/kg/day cyclosporine with emollient

600 placebo ointment (87% vs 37%; p=0.0001).[150]

601 **Table 23**. *Recommendation and strength of recommendation for combination of topical agents*

602 *and cyclosporine*

Recommendation Number	Recommendation	Strength of Recommendation
11.1	The addition of calcipotriene/betamethasone dipropionate ointment to low dose (2 mg/kg/day)	B

	cyclosporine can be used for the treatment of moderate to severe psoriasis	

Table 24. *Level of evidence for the combination of topical agents and cyclosporine*

Recommendation	Recommendation Number	Level of Evidence	Studies
Cyclosporine and calcipotriene/betamethasone dipropionate for psoriasis	11.1	I	[150]

Topical calcipotriene & acitretin

The addition of calcipotriene ointment to standard dose acitretin can improve the efficacy of acitretin. A multicenter RCT of 135 adults with severe psoriasis demonstrated a greater rate of clearance and marked improvement in the combination group compared with acitretin alone (67% vs 41%; p=0.006).[4] There were no differences in safety between the two groups.[4]

Table 25. *Recommendation and strength of recommendation for the combination of calcipotriene and acitretin*

Recommendation Number	Recommendation	Strength of Recommendation
12.1	The addition of calcipotriene to standard dose acitretin is recommended for the treatment of moderate to severe psoriasis.	A

Table 26. *Level of evidence for the combination of calcipotriene and acitretin*

Recommendation	Recommendation Number	Level of Evidence	Studies
Calcipotriene and acitretin for psoriasis	12.1	I	[4]

Role of patient preference

Role of patient preferences – with topical agents

The optimal vehicle choice is often the one the patient is most likely to use. For example, hair-bearing areas such as the scalp are often successfully treated with solutions,

shampoos, foams, oils, gels, or sprays. In general, creams are more cosmetically acceptable than ointments for glabrous skin. Nevertheless, some patients do prefer ointments.

It is recommended that clinicians take into account patient preference when selecting the most appropriate vehicle, recognizing different vehicles may have a different clinical impact on patients and their adherence to treatment. It is important for the healthcare provider to be aware of the different vehicles available to provide the best option for each patient on a case-by-case basis.

Compounding of topical agents

Compounding by reputable pharmacies of topical agents is frequently used in clinical practice and is beneficial in certain patients pending the quality of the ingredients and the quality of the compounding.

This concludes the portion of the AAD-NPF joint guideline on care for the management of psoriasis with topical therapy. The following section of this joint guideline will focus on the use of alternative medicine (AM) for the treatment of psoriasis. The workgroup provided their expert opinion on AM therapy and is not part of evidence-based recommendations. Furthermore, the joint guideline also discusses the severity measures of psoriasis used in clinical practice and trials as well as patient-reported outcomes.

II. ALTERNATIVE MEDICINE (AM)

Alternative medicine (AM) can be defined as a set of products and practices that are believed to have similar or better healing effects than allopathic medicine. Nevertheless, in many cases, their effectiveness may not have been established using scientific methods or may have not shown similar or superior results compared to conventional medications. Alternative medicine

is not typically part of conventional medical care or that have origins outside of usual Western practice and maybe desired by, and of benefit to, a subset of patients. Complementary alternative medicine (CAM) consists of the use of alternative medicine together with conventional medical treatment, based on the belief that it improves the effect of medical treatments.

Traditional Chinese Medicine (TCM)

Efficacy

Traditional Chinese Medicine (TCM) is an approach commonly utilized in China for patients of varying psoriasis severity and includes topical and oral herbs as well as acupuncture and other therapeutic modalities. Herbal methods should only be considered and incorporated if the ingredients within the herbal blends are known and well-understood. Acupuncture has been used for the therapy of psoriasis, especially mild-moderate with responses relatively minor. Several clinical trials have assessed the efficacy of herbal medicine (HM) for the treatment of psoriasis. A systematic review of topical HM for the treatment of psoriasis found that Mahonia aquifolium, indigo naturalis, and Camptotheca sp. showed anti-inflammatory benefits compared to the vehicle. Adding these topical HMs to conventional pharmacotherapy appeared to produce additional clinical benefits. Nevertheless, the author mentions the lack of standardization as a weakness of the included studies and states further research is needed to assess the efficacy and safety of these HMs as adjunct therapies for psoriasis.[151] An RCT assessed the efficacy of indigo naturalis extract in oil (lindioil) vs olive oil for the treatment of nail psoriasis. After 12 weeks of twice-daily treatment, there was a significant difference in NAPSI reduction for one hand; 48.9% for the lindioil group vs 22.9% for the olive oil group.[152]

A randomized clinical trial with 56 psoriasis patients assessed the efficacy of electrostimulation by intramuscularly placed needles plus ear-acupuncture or placebo (minimal acupuncture) twice weekly for 10 weeks. After 10 weeks of treatment, the mean PASI had decreased from 9.6 to 8.3 in the 'active' group and from 9.2 to 6.9 in the placebo group ($p<0.05$ for both groups) with no statistically significant differences between the two groups. The benefit seen with minimal acupuncture may indicate a positive placebo effect from the perception of attention paid to the patient, and mere interest in a holistic approach on the part of a practitioner.[153]

A single-blind RCT compared “auricular therapy” (pressure and blood-letting puncture of the auricular points on the back of the ear) plus optimized Yinxieling formula with Yinxieling formula alone in 84 psoriasis patients. Optimized Yinxieling formula is composed of Radix paeoniae rubra, Rhizoma curcumae, sarcandra, Radix glycyrrhizae, Fructus mume, Radix arnebiae, and Rhizoma smilacis glabrae. After 8 weeks of treatment, the PASI reduction in the combination treatment group was 74.4% (32/43), compared to the optimized Yinxieling formula alone group (36.6%, $P<0.01$).[154]

An open-label RCT with 60 psoriasis patients utilizing Yin Xie Ping granules vs Xiao Yin Pian (known HM to treat psoriasis as control) found no significant difference between two groups.[155] The clinical improvement determined as cured and markedly effective was achieved by 61.67% and 50% patients in Yin Xie Ping and control group, respectively. Yin Xie Ping is compounded with Radix rehmanniae, Radix angelicae formosanae, powder of Carapax eretmochelys, Radix paeoniae rubra, Calculus bovis artificial, and Herba schizonepetae tenuifoliae. Xiao Yin Pian is compounded with Radix rehmanniae, Cortex moutan, Radix paeoniae rubra, Sophora flavescens, honeysuckle, Radix sappan, Arctium lappa, Folium isatidis, and safflower.

A systematic review of studies comparing phototherapy (UVA and UVB) with and without herbal baths showed that herbal baths appeared to improve response to phototherapy, but the lack of standardization makes results difficult to interpret and replicate.[156] The HM formula used for the bath varied across the 13 studies analyzed. The most frequently used herbs were Salvia miltiorrhiza root, Dictamnus dasycarpus bark, Sophora flavescens root, and Kochia scoparia fruit. The HM bath was taken for 20 to 30 minutes before each phototherapy session.

Risks/Harms and Benefits

Constituent herbs can be difficult to elucidate in Chinese herbal blends, thereby making allergy and toxicity risk difficult to predict. Some formulations of herbal remedies have been found to contain corticosteroids.[157,158] Topical indigo naturalis must be carefully formulated by a compounding or integrative pharmacist to minimize the natural purple staining effect of the crude extract.

Exclusions

There is little information on the effects of herbal medicine and psoriasis during pregnancy or lactation. Because of the unknown effects on the fetus or infant, they should be avoided during pregnancy and breastfeeding and if there is a known allergy to prevent potential toxicity from herbal blends.

Role of patient preferences

Many patients undergo acupuncture for a variety of health reasons. Several insurance companies reimburse for acupuncture. Interest on the part of patients is high.[159]

General Comments

TCM is by definition an individualized medical practice based on each patient's constitution and therefore is difficult to study in an aggregate model. Additionally, the lack of standardized clinical trials makes it very difficult to clearly assess the efficacy of these treatments. Understanding TCM requires an intense background in herbology, which is lacking in traditional allopathic medical curricula.

Aloe Vera

Efficacy

Aloe vera (AV) is a succulent plant species of the genus Aloe. Its use has been documented in medicine for centuries. In patients who are not allergic to AV, topical AV may be efficacious for mild psoriasis. An RCT with 60 psoriasis patients comparing three times daily application of AV vs placebo for 4 weeks reported 83.3% cure rate (complete clearance) in the AV group vs 6.6% in the placebo group.[160] A double-blind RCT with 40 patients assessing AV vs placebo showed no difference between the two groups after 4 weeks of twice-daily application.[161] Furthermore, the clinical score sum of erythema, infiltration, and desquamation decreased in 72.5% in the AV treated areas compared with 82.5% in placebo-treated areas after 12 weeks.[161] Despite the placebo effect being elevated and higher than that of AV, the clinical effect of AV was not negligible. Nevertheless, it should be noted that AV might not be better than just an emollient. Additionally, topical and oral use of AV can cause skin irritation, hives, cramping, and diarrhea to those who are allergic to other plants in the lily family, for example, onion and tulips.[162,163]

Risks/Harms and Benefits

There is a risk of contact dermatitis with AV use.

Contraindication

Treatment should not be utilized in patients who are allergic to AV.

Role of patient preferences

For patients who are interested in trying a plant-based treatment for their mild psoriasis, AV may be a reasonable consideration.

St John's Wort

Efficacy

Topical St John's wort may improve mild psoriasis, but its compounding is not standardized or well-studied enough to recommend its use. There is limited literature on this subject. A split body study with compounded topical St John's wort cream showed a significant modified PASI reduction at 4 weeks compared to vehicle alone ($P<0.04$).[164] This study demonstrated a reduction in erythema, lesional thickness, and scaling over 4 weeks.

Risks/Harms and Benefits

Due to St. John's wort photosensitizing effect, caution exists for burns and sunburns, especially for psoriasis patients undergoing phototherapy.

Exclusions

St John's wort is photosensitizing when administered topically and orally. Caution should be exercised in patients with a history of skin cancer and/or continued heavy sun exposure, including phototherapy. Safety in pregnant and nursing women is unknown.

Role of patient preferences

Considering an increasing number of patients asking about non-prescription and natural options for psoriasis, further studies are required to better assess the role of St John's wort in psoriasis.

General Comments:

As St John's wort is a supplement that is generally used for potential anti-depressive effects, a potential therapeutic role in psoriasis may also exist in the area of stress reduction if taken orally.

Fish/Omega-3 Oil

Efficacy

Fish oil may exert an anti-inflammatory effect via inhibition of inflammatory eicosanoid formation. Fish oil/omega 3 fatty acid oral supplementation has been useful as a monotherapy for psoriasis.[165,166] Oral fish oil supplementation may augment the effects of topical, oral-systemic, and phototherapy for chronic plaque psoriasis. It can be considered as an additional supplement in patients with chronic plaque psoriasis.[167-171] Fish oil can be useful as adjuvant therapy for treatments including acitretin, cyclosporine, and NBUVB.[172,173] A randomized 12-week open study revealed that etretinate and eicosapentaenoic acid supplementation for patients with chronic stable plaque psoriasis had better and more rapid improvement compared to etretinate alone.[174]

Risks/Harms and Benefits

Due to contaminants, fish oil supplementation can cause mercury poisoning or accumulation of other toxins such as dioxins and polychlorinated biphenyls (PCB).[175-177]

Exclusions

Caution should be exercised in pregnant women. Patients should be instructed to select supplements that are free of mercury, dioxin, and PCB. While fish oil can reduce platelet aggregation, this effect did not increase bleeding risk during or after surgery in randomized clinical trials.[178,179]

Role of patient preferences

Considering an increasing number of patients frequently asking about non-prescription and natural treatment options for psoriasis, further studies are required to better assess the role of fish oil supplementation/omega-3 fatty acids in psoriasis.

Vitamin D supplementation

Efficacy

While topical vitamin D analogues have benefit in psoriasis, oral supplementation does not directly improve disease activity at dosages that avoid hypercalcemia and calciuria.[180-184] Therefore, oral vitamin D supplementation is not recommended for the treatment of psoriasis.[184]

Risks/Harms and Benefits

Excess vitamin D supplementation may lead to hypercalcemia.

Precaution

Studies here reviewed do not include pregnant or lactating women or children.

Role of patient preferences

Many patients ask about the overall role of vitamin D in skin health. Rather than adding oral vitamin D supplementation, topical therapy with Vitamin D agents is effective for the treatment of psoriasis.

Curcumin

Efficacy

Curcumin is the active chemical in the spice turmeric. Curcumin modulates T helper type 22 cell activity and decreases epidermal proliferation via inhibition of ATP-phosphorylase b phosphotransferase activity, similar to topical vitamin D3 analogues.[185] While there is limited literature on this subject, oral curcumin supplementation may benefit patients with psoriasis as adjunctive therapy.

Risks/Harms and Benefits

Curcumin has low toxicity but poor bioavailability.

Role of patient preferences

Patients increasingly ask about non-prescription or natural options for psoriasis. Further studies are required to better assess the role of curcumin in psoriasis.

Zinc

Efficacy

There is limited literature on the efficacy of zinc for the treatment of psoriasis. Oral zinc supplementation did not independently improve psoriasis severity (PASI scores) and therefore is not recommended.[186]

Risks/Harms and Benefits

Oral zinc has been associated with headaches, nausea, vomiting, decreased appetite, diarrhea, and abdominal cramps.[187] In high doses with prolonged use can have more severe adverse effects such as low copper, anemia, leukopenia, neutropenia, and GI ulcers.[187]

Role of patient preferences

Patients are increasingly interested in taking oral supplements. Further studies are required to better assess the role of zinc supplementation in psoriasis.

Gluten-free diet (GFD)

Efficacy

Gluten is a group of proteins present in various cereal grains that are associated with hypersensitivity and celiac disease in certain patients. A small percentage (4-14%) of patients with moderate to severe plaque psoriasis have a higher incidence of celiac disease and therefore should be asked about gastrointestinal (GI) symptoms of celiac disease.[188-191] If patients have a positive serology for the disease or have GI symptoms of celiac disease, consultation with a gastrointestinal physician to confirm celiac disease with small intestine biopsy and manage the disease is advised. Adherence to a gluten-free diet (GFD) is part of the treatment plan only for patients with confirmed celiac disease.[191-193]

Patients testing positive to celiac antibodies may not benefit from a strict GFD in terms of PASI improvement, because they may not have actual celiac disease. The diagnosis of celiac disease is not just based on symptoms and serology and patients should be referred to a gastroenterologist for diagnosis and management. For patients who are already following restricted diets (vegetarian, vegan, nut-free, etc.) due to personal choice or other medical

conditions (including food allergies), and are now planning to eliminate gluten, consultation with a nutritionist is strongly suggested to optimize nutrition and assist in meal planning. A gluten-free diet is inadvisable from a psoriasis treatment perspective unless the patient has a confirmed diagnosis of celiac disease.

Role of patient preferences

Patients often ask about the role of diet in skin health, and many would be interested in incorporating a gluten-free diet if applicable and potentially beneficial. Others would find this diet a detriment to their quality of life.

Hypnosis

Efficacy

Hypnosis is a state characterized by focused attention and an increased capacity to respond to suggestions. Hypnosis should be considered a therapeutic adjunct for highly hypnotizable patients with mild to moderate psoriasis. However, there is limited literature on this subject. A small pilot trial in 11 psoriasis patients showed a significant improvement in PASI score and attainment of PASI 75 compared to neutral hypnosis after 3 months of weekly hypnosis ($p<0.001$).[194]

General comments

These recommendations would not apply to patients who are not highly hypnotizable. Access to a trained hypnotherapist would limit the ability to incorporate this therapy.

Role of patient preferences

Patients must be interested in and amenable to hypnosis optimal benefit. Further studies are required to better assess the role of hypnosis in psoriasis.

Stress reduction

Efficacy

Stress reduction includes a wide spectrum of techniques aimed at controlling a person's stress level. Meditation as a form of stress reduction can have a positive impact on the severity of symptoms in some patients with psoriasis. Therefore, it can be discussed as adjunctive therapy with interested patients. A small study assessing different meditation techniques as adjunctive therapy in mild to moderate psoriasis patients treated with topical therapies showed improvement of psoriasis symptoms after 12 weeks compared to no adjunctive treatment.[195] There is evidence that guided mindfulness meditation improves outcomes in patients with moderate psoriasis qualifying for phototherapy.[196] Biofeedback and relaxation techniques (progressive and suggestive) may improve symptoms in some patients with mild psoriasis and should also be considered for adjunctive therapy.[197] Psychologic interventions in the form of stress reduction techniques, cognitive behavioral therapy, and guided imagery can improve psoriasis severity and should be discussed with all interested patients.[198] Data are limited on this subject and further research is needed.

Risks/Harms and Benefits

While studies are limited and data are lacking, individual treatment responses are positive with little to no adverse effect of these adjunctive recommendations (expert opinion).

Work and other time constraints may be a limiting factor for some patients to engage in a guided meditation or relaxation strategies but interested patients can be taught a self-guided practice which can be tailored to any schedules.

Biofeedback is time-consuming and requires specialized equipment.

872 ***Role of patient preferences***

873 Patients' interest in, and receptiveness to, mindfulness meditation practices may influence the

874 degree of therapeutic efficacy. Further studies are required to assess the role of stress

875 reduction in psoriasis.

876 **Table 27.** Supplementary statements for complementary alternative medicine*

Therapy	Statement	Studies
Traditional Chinese Medicine (TCM)*	Herbal methods should only be considered and incorporated if herbal blends are well-understood and if working with practitioners experienced in dermatology and in TCM.	151-156,199-202
	Acupuncture may have a therapeutic effect on chronic plaque psoriasis and can be considered as adjunctive therapy in psoriasis based on patient interest and practice availability	
	Risk/Harm & Benefits • Topical indigo naturalis must be carefully formulated by a compounding or integrative pharmacist to avoid the natural purple staining effect of the crude extract • Constituent herbs can be difficult to elucidate in Chinese herbal blends, thereby making allergy and toxicity difficult to predict • The benefit seen with "sham" acupuncture may indicate a positive placebo effect from the perception of attention paid to the patient, and mere interest in a holistic approach on the part of a practitioner **Exclusions** • Safety in pregnancy and breastfeeding are unknown. Potential allergy and toxicity risk exist from undifferentiated herbal blends	
Aloe Vera*	In patients who are not allergic, topical aloe vera may have efficacy in the treatment of mild psoriasis	160,161
	Risk/Harms and Benefits • There is a risk of contact dermatitis in patients who	

* Supporting suggestions are not evidence based

Therapy	Statement	Studies
	use aloe vera **Exclusions** • Treatment should not be utilized in patients who are allergic to aloe vera	
St. John's Wort*	Topical St John's wort may lower PASI Score, but is not standardized, commercially available or well-studied enough to recommend its use	164
	Risk/Harms and Benefit • Due to the photosensitizing effect, caution exists for burns and sunburns, especially for psoriasis patients undergoing phototherapy **Exclusions** • St John's wort is known to be photosensitizing if taken orally and this same consideration exists for topical administration. Caution should be exercised in patients with a history of skin cancer and/or continued heavy sun exposure, including phototherapy. Safety in pregnant and nursing women is unknown	
Fish Oil*	Fish oil/omega 3 fatty acid supplementation is not useful as monotherapy, but may augment the effects of other topical and oral-systemic therapies and phototherapy for chronic plaque psoriasis and may be considered in those patient populations	165,167-169,171-174,203,204
	Risk/Harms and Benefits • Due to contaminants, fish oil supplementation can cause mercury poisoning or accumulation of other toxins such as dioxins and polychlorinated biphenyls (PCBs) **Exclusions** • Caution should be exercised in pregnant women. Patients should be instructed to select supplement sources that are free of mercury, dioxin, and PCBs (polychlorinated biphenyls). The risk of bleeding with fish oil has been generally determined to be not real	
Vitamin D supplementation*	While it is established that topical vitamin D analogues have benefit in psoriasis, oral supplementation does not directly improve disease activity at dosages that avoid hypercalcemia and calciuria	180,183,205,206
	Risk/Harms and Benefits • Excess vitamin D supplementation may lead to	

Therapy	Statement	Studies
	toxicity in the form of hypercalcemia **Exclusions** • Role of Vitamin D oral supplementation in pregnant/lactating women or children not included.	
Curcumin*	Oral curcumin supplementation may benefit patients with psoriasis of varying severity, as adjunctive therapy	185,207-209
Zinc*	Oral zinc supplementation does not improve PASI scores	186
Gluten-Free Diet*	Patients with moderate to severe plaque psoriasis may, but not always have a higher incidence of celiac disease and therefore should be asked about GI symptoms of celiac disease. If identified positive, consultation with GI physician for treatment and management of the disease is advised. Further, adherence to a gluten-free diet is suggested to be part of the treatment plan only for patients diagnosed with celiac disease	188-193,210-212
	Risk/Harm and Benefits • Patients testing positive to celiac antibodies may benefit from a strict gluten-free diet in terms of PASI improvement, but also may not. A trial period of 3 months should be considered. Gluten-free diets are restrictive and can impact the quality of life **Exclusions** • For patients who are already following restricted diets (vegetarian, vegan, nut-free, etc.) due to personal choice or food allergies and are now planning to eliminate gluten, a nutritionist should be consulted in order to best plan meals and avoid nutritional deficiencies	
Hypnosis*	Hypnosis can be discussed with and incorporated as a therapeutic adjunct for highly hypnotizable patients with mild to moderate psoriasis	194
Stress Reduction*	Meditation as a form of stress reduction can have a positive impact of severity of symptoms in some patients with psoriasis and therefore could be discussed as adjunctive therapy with interested patients	195,196,198,213
	Mindfulness meditation (guided) improves outcomes in patients with moderate psoriasis qualifying for phototherapy	
	Biofeedback and relaxation techniques (progressive and suggestive) may improve symptoms in some patients with mild psoriasis and should be considered for adjunctive therapy	

Therapy	Statement	Studies
	Psychologic interventions in the form of stress reduction techniques, cognitive behavioral therapy, and guided imagery can improve psoriasis severity and should be discussed with all interested patients	
	Risk/harm and Benefits • Work and other time constraints may be a limiting factor for some patients to engage in a guided meditation or relaxation strategies but interested patients can be taught a self-guided practice which can be tailored to any schedule • Biofeedback is time-consuming and requires specialized equipment	
Other AM therapies	Turmeric, cannabis, and cannabinoids are not infrequently used by patients. Not enough literature is available to justify their usage	

This concludes the portion of the AAD-NPF joint guideline on AM. The following section of this joint guideline will focus on severity measures for psoriasis.

III. PSORIASIS SEVERITY MEASURES

Body surface area (BSA)

Recommendations

Body surface area (BSA), one of the most commonly used measures in clinical and research dermatology, is recommended to assess the severity of psoriasis as well as the response to treatment in the clinical setting.[214-218] It is calculated by using the area from the wrist to the fingers and thumb of the hand closed together to represent ~1% of the patient's BSA.[219] Its use can be simplified by rounding up the percentage of BSA corresponding to different parts of the body. The head and neck, upper extremities, trunk, and lower extremities

888 (including buttocks) correspond to approximately 10%, 20%, 30%, and 40% of the BSA,
889 respectively. Refer to *AAD pay-for-performance Measure 410* for further details.[219†]

890 Patient preferences play a primary role in determining the final treatment target and
891 treatment. A full discussion should be offered to the patient regarding the treatment options
892 and expected benefits, risks, and outcomes in order to facilitate a shared decision-making
893 approach.

894 The re-assessment of disease severity and response to therapy can be performed
895 regularly and adjustments to therapy as necessary. In particular, if the patient is dissatisfied
896 with clinical responses, a different therapy should be considered. Individual patient preferences
897 and comorbidities are important in the final treatment plan. If a patient is satisfied with their
898 results, they should continue treatment even if it does not meet the target or recommended
899 improvement.

900 ***Pitfalls (or limitations) in assessment***

901 BSA can be over-estimated, particularly by untrained providers.[220-224] Nevertheless, BSA
902 assessment has good intra-rater reliability.[215,225]

903 The BSA measurement is a provider assessment tool. It does not take into account
904 location on the body, clinical characteristics of the plaques, symptoms, or quality of life issues.

905 ***Table 28.*** *Recommendation and strength of recommendation for BSA severity measure*

Recommendation Number	Recommendation	Strength of Recommendation
13.1	Body surface area (BSA) measurement of involved skin is recommended as an important measure of psoriasis severity to risk stratify patient for future	B

† https://www.aad.org/member/practice/mips/measures/410

	co-morbidities and to assess response to treatment	

Table 29. *Level of evidence for BSA severity measure*

Recommendation	Recommendation number	Level of evidence	Studies
BSA for severity assessment of psoriasis	13.1	II-III	Expert Opinion

Psoriasis Area and Severity Index (PASI)

Recommendations

PASI assesses 3 plaque issues (erythema, induration, and scaling) plus the body surface area affected and provides a severity score ranging from 0 to 72. In general, a score of ≥10 is considered moderate to severe psoriasis.[219] Refer to *AAD pay-for-performance Measure 410* for further details.[219‡] PASI is recommended as a measure of psoriasis severity and response to treatment for moderate to severe psoriasis primarily in clinical trials. PASI is primarily a research tool, and its use in clinical practice is infrequent.[216,217,226-230]

Pitfalls (or limitations) in assessment

Various studies have revealed that PASI has reproducible inter-rater and intra-rater reliability.[231-233] Rater experience reduces the variation in the scores.[234,235] Delta of mean PASI and delta of mean Dermatology Life Quality Index (DLQI), quality of life assessment tool designed for dermatological conditions, are highly correlated and showed improvement over a prolonged period of time (6.5 years) when treated with biologics.[236] PASI is responsive to varying degrees of improvement in psoriasis.[237] Additionally, PASI is more strongly correlated with clinical response to initiating biologic therapy than DLQI.[238,239] Nevertheless, PASI is not accurate for mild psoriasis, defined as below 3% BSA affected. The average psoriasis patient will

‡ https://www.aad.org/member/practice/mips/measures/410

not have BSA measurements as high as those in clinical trials and research. Furthermore, PASI is not ideal for measuring certain aspects of the disease such as nail, palmoplantar, and genital psoriasis. PASI is not an easily accessible tool to use due to time intensiveness. Thus, PASI is not a frequently used tool in clinical practice.

General Comments

The PASI is a provider assessment tool. PASI has significant evidence as a useful tool in research settings but does not take into account symptoms or quality of life issues.

Table 30. *Recommendation and strength of recommendation for PASI severity measure*

Recommendation number	Recommendation	Strength of recommendation
14.1	Psoriasis area and severity index (PASI) is a commonly used outcome measure in clinical trials. However, it is seldom used in clinical practice to assess the severity	B

Table 31. *Level of evidence for PASI severity measure*

Recommendation	Recommendation number	Level of Evidence	Studies
PASI severity assessment tool	14.1	III	216,217,226-229

Physician Global Assessment (PGA)

Recommendations

The Physician Global Assessment (PGA) is a scoring system that uses erythema, induration, and scaling. It is suggested as an important measure to assess psoriasis severity and response to treatment.[216,233,234,237,240,241] There are several different PGA versions with most severity scores ranging from 0-4 or 0-5.[219] In many clinical trials and research, it is used as a primary endpoint but its use in clinical practice, while potentially valuable, is infrequent.

The re-assessment of disease severity and response to therapy can be performed at intervals and adjustments to therapy as necessary. Refer to *AAD pay-for-performance Measure 410* for further details.[219§]

Individual patient preferences and comorbidities are important regarding the final treatment plan. If a patient is satisfied with their results, they should be allowed to continue treatment even if it does not meet the target or recommended improvement.

Pitfalls (or limitations) in assessment

PGA has reproducible inter-rater and intra-rater reliability and validity.[233,234,241] PGA is responsive to varying degrees of clinical improvement.[237] Additionally, PGA and Lattice System-PGA (LS-PGA) do not require significant experience to achieve reliable results.[234] Plaque quality/morphology does not account for the body surface area or the widespread nature of the disease. This is a limitation of the PGA systems.

General Comments

The PGA is an assessment tool and a relatively simple tool to grade and use. It may represent a static measure of the physician's impression at a single point or a dynamic measure in which the physician assesses global improvement from baseline. The PGA does not take into account symptoms or quality of life issues.

Table 32. *Recommendation and strength of recommendation for PGA severity measure*

Recommendation number	Recommendation	Strength of recommendation
15.1	Physician global assessment (PGA) measurement of psoriasis is suggested as an important measure to	B

§ https://www.aad.org/member/practice/mips/measures/410

	assess psoriasis severity	

Table 33. *Level of evidence for PGA severity measure*

Recommendation	Recommendation number	Level of Evidence	Studies
PGA for severity assessment of psoriasis	15.1	I-III	216,233,234,237,240,241

PGA x BSA

Recommendations

Physician Global Assessment x Body Surface Area (PGAxBSA) can be used as a measure of psoriasis severity and response to treatment. it is not commonly used although a few dermatologists do use it in clinical practice.

Individual patient preferences and comorbidities are important regarding the final treatment plan. As such, if a patient is satisfied with their results, they should be allowed to continue treatment even if it does not meet the target or recommended improvement.

Pitfalls (or limitations) in assessment

BSA can be over-estimated, particularly by untrained providers.[220-224] Nevertheless, BSA assessment has good intra-rater reliability.[215,225] PGA has reproducible inter-rater and intra-rater reliability and validity.[233,234,241] PGA is responsive to varying degrees of clinical improvement.[237] The BSA measurement is a provider assessment tool. It does not take into account location on the body, clinical characteristics of the plaques, symptoms, or quality of life issues. Furthermore, the combination of two measures adds an extra step that could be detrimental for the practical use of this tool in the clinical setting.

Table 34. *Recommendation and strength of recommendation for PGA x BSA severity measure*

Recommendation number	Recommendation	Strength of recommendation
16.1	Physician global assessment x Body surface area	B

	(PGAxBSA) is recommended as an important measure of psoriasis severity	

Table 35. *Level of evidence for PGA x BSA severity measure*

Recommendation	Recommendation number	Level of Evidence	Studies
PGAxBSA for the assessment of psoriasis severity	16.1	II	[242-244]

Psoriasis Symptom Inventory (PSI)

Recommendations

The Psoriasis Symptom Inventory (PSI) is a new patient-reported outcome, which has been validated in clinical studies and has the potential to be used in clinical practice.[245-249] The PSI measures the severity of eight psoriasis signs and symptoms: itch, redness, scaling, burning, stinging, cracking, flaking, and pain. Each item is rated on a scale of 0 to 4, yielding a total score ranging from 0 to 32.

Pitfalls (or limitations) in assessment

As a patient-reported outcome, the PSI relies on patients being willing and able to complete the assessment. For patients with cognitive impairment, the PSI may not be feasible or reliable.

General Comments

There are paper versions of the PSI available for patient use.[245,248]

Table 36. *Recommendation and strength of recommendation for PSI severity measure*

Recommendation number	Recommendation	Strength of recommendation
17.1	The Psoriasis Symptom Inventory (PSI) is recommended as an important patient-reported measure of psoriasis severity with utility in clinical trials. PSI is a new quality of life instrument and has	C

	potential to be used in clinical practice and clinical trials	

991 ***Table 37****. Level of evidence for PSI severity measure*

Recommendation	Recommendation number	Level of Evidence	Studies
PSI for severity assessment of psoriasis	17.1	I-II	[245-248]

992 **Dermatology Life Quality Index (DLQI)**

993 ***Recommendations***

994 The Dermatology Life Quality Index (DLQI) is a ten-question questionnaire used to
995 measure the impact of skin disease on the quality of life of an affected person. The DLQI score
996 ranges from 0 to 30. It is a self-reported measure of psoriasis that is recommended to assess
997 psoriasis severity and response to treatment with utility in clinical trials.[219] Refer to the *AAD*
998 *pay-for-performance Measure 410* for further details.[219**] DLQI is used in over 40 different skin
999 condition and is not a specific measurement tool for psoriasis.[216,217,226-229,250-254]

1000 ***Pitfalls (or limitations) in assessment***

1001 As a patient-reported outcome, the DLQI relies on patients being willing and able to
1002 complete the assessment. For patients with cognitive impairment, the DLQI may not be feasible
1003 or reliable.

1004 ***General Comments***

1005 The DLQI is a patient-reported severity measure used in over 40 different skin
1006 conditions and in the majority of clinical trials in moderate-severe psoriasis.[219] It is readily used
1007 in over 80 countries and available in more than 85 languages.[219]

1008 ***Table 38.*** *Recommendation and strength of recommendation for DLQI severity measure.*

** https://www.aad.org/member/practice/mips/measures/410

Recommendation number	Recommendation	Strength of recommendation
18.1	Dermatology Life Quality Index (DLQI) measurement of psoriasis is recommended as an important measure of psoriasis severity with utility in clinical trials and is seldom used in clinical practice.	B

Table 39. *Level of evidence for DLQI severity measure*

Recommendation	Recommendation number	Level of Evidence	Studies
DLQI is a research tool used in clinical trials	18.1	II-III	226,227,250-254

Pruritus assessment

Recommendations

Pruritus is a significant symptom of psoriasis and is often under-recognized. Itch severity assessment is recommended for patients whose psoriasis causes significant pruritus as it can have a major impact on a patient's quality of life. There are several tools available to assess this subjective symptom.[255-271] Nevertheless, at this time there is no recommendation on which tool should be used due to limited evidence. The Visual Analog Scale (VAS) and Numeric Rating Scale (NRS) are two of the most commonly used pruritus assessment tools. When assessing patients with these two scales, the minimal clinically important difference (MCID) should be 3 – 4 points for a change to be considered meaningful.[272-274]

Table 40. *Recommendation and strength of recommendation for pruritus assessment severity measure*

Recommendation number	Recommendation	Strength of recommendation
19.1	Pruritus is a significant symptom of psoriasis. An itch severity assessment is recommended to appropriately assess the degree of pruritus when present	B

Table 41. *Level of evidence for pruritus assessment severity measure*

Recommendation	Recommendation number	Level of Evidence	Studies
Itch severity assessment for patients with psoriasis	19.1	II-III	255-271

In conclusion, there is no one measure to completely determine a patient's quality of life. Some patients may have a low severity score, but the affected area may be in a very sensitive location such as the face or hands. This may require escalating the treatment used to treat psoriasis depending on patient preference. Therefore, it is important to work with the patient to determine their satisfaction with the treatment. Similarly, some patients may not be comfortable with certain methods of administration. In these cases, it is also important to work with the patient to determine a treatment modality they are comfortable with. For example, some patients may not like using needles, therefore any treatment relying on needles for self-administration may not be as effective for the patient. Working with the patient will increase adherence to the treatment protocol. There may also be cases in which the patient is satisfied with a less than "clear" outcome. In these cases, it would be necessary to work with the patient to determine what outcome they are satisfied with based on their preferences.

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APPENDIX

Methods

A multidisciplinary work group (WG) of psoriasis experts consisting of dermatologists (including private practitioners), a rheumatologist, a cardiologist and representatives from a patient advocacy organization, was convened to update and expand on the previously published 2008 AAD psoriasis guideline.[127] The WG determined the scope of the guideline and identified important clinical questions with regard to psoriasis treatment with topical agents and AM (Table I). WG members completed a disclosure of interests that was periodically updated and reviewed for potentially relevant conflicts of interests throughout guideline development. If a relevant conflict was noted, a balance of conflicted and non-conflicted WG members was used to draft initial recommendations.

An evidence-based model was used, and evidence was obtained using a search of the PubMed and MEDLINE databases from January 1, 2008 to December 31, 2017 for clinical questions addressed in the previous version of this guideline published in 2008-2011, and for all newly identified clinical questions. Searches were limited to publications in the English language. MeSH terms used in various combinations in the literature search included: psoriasis (vulgaris, plaque, guttate, erythrodermic, pustular, palmoplantar, inverse, nail); topical corticosteroids, calcipotriol, calcineurin inhibitors (Tacrolimus, Pimecrolimus), combination, switch, failure (primary, secondary), alternate, cessation, emollients, salicylic acid, anthralin, body surface area (BSA), psoriasis area and severity index (PASI), physician global assessment (PGA), psoriasis symptom inventory (PSI), dermatology of life quality index (DLQI), pruritus

assessment, traditional Chinese medicine, aloe vera, St. John's Wort, Fish oil, Vitamin D, Turmeric (Curcumin), Zinc, Hypnosis, meditation, stress reduction.

After removal of duplicate data, 287 (157 [Topical], 66 [Severity Measures], 64 [AM]) articles were retained for final review based on relevancy and the highest level of available evidence for the outlined clinical questions. Evidence tables were generated for these studies and utilized by the work group in developing recommendations. The Academy's prior published guidelines on psoriasis were evaluated, as were other current published guidelines on psoriasis as part of evidence review.

The available evidence was evaluated using a unified system called the Strength of Recommendation Taxonomy (SORT) developed by editors of the US family medicine and primary care journals (i.e. American Family Physician, Family Medicine, Journal of Family Practice, and BMJ USA). Evidence was graded using a 3-point scale based on the quality of methodology (e.g. randomized controlled trial, case-control, prospective/retrospective cohort, case series, etc.) and the overall focus of the study (i.e. diagnosis, treatment/prevention/screening, or prognosis) as follows:

I. Good-quality patient-oriented evidence (i.e. evidence measuring outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life)

II. Limited-quality patient-oriented evidence

III. Other evidence including consensus guidelines, opinion, case studies, or disease-oriented evidence (i.e. evidence measuring intermediate, physiologic, or surrogate end points that may or may not reflect improvements in patient outcomes)

Clinical recommendations were developed on the best available evidence tabled in the guideline. These are ranked as follows:

A. Recommendation based on consistent and good-quality patient-oriented evidence

B. Recommendation based on inconsistent or limited-quality patient-oriented evidence

C. Recommendation based on consensus, opinion, case studies, or disease-oriented evidence

In those situations where documented evidence-based data is not available, we have utilized expert opinion to generate our clinical recommendations or opted not to issue a recommendation.

This guideline has been developed in accordance with the American Academy of Dermatology (AAD)/AAD Association Administrative Regulations for Evidence-based Clinical Practice Guidelines (May 2014)[275], which includes the opportunity for review and comment by the entire AAD membership and final review and comment by the AAD Board of Directors. Additionally, this guideline is developed in collaboration with the National Psoriasis Foundation (NPF) and as part of the review process; the NPF medical board members provided their feedback. This guideline will be considered current for a period of five years from the date of publication unless reaffirmed, updated or retired before that time.

DEFINITION

Psoriasis vulgaris is a chronic inflammatory skin disease which classically presents with well-demarcated, red plaques with silvery scale, commonly involving the scalp, elbows, knees,

and pre-sacral region, though any area of skin may be involved, including the palms, soles, nails, and genitalia. While the severity of psoriasis is defined in part by the total body surface area (BSA) involved, with less than 3% BSA considered mild, 3-10% BSA considered moderate, and greater than 10% considered severe disease, psoriasis can be severe irrespective of BSA, when it has serious emotional consequences or when it occurs in select locations, including, but not restricted to, the hands, feet, scalp, face, genital area, or when it causes intractable pruritus. The Psoriasis Area Severity Index (PASI) is a more specific means of quantifying the extent and severity of psoriasis, as it takes into account not only BSA but also the intensity of redness, scaling, and plaque thickness, ultimately producing a score from 0 (no disease) to 72 (maximal disease severity). The PASI is used for monitoring response to treatments in clinical trials, and as a research tool to judge the severity of psoriasis. It is rarely utilized by dermatologists in clinical practice to guide management.

Psoriasis is an inflammatory, immune-mediated condition involving cutaneous T-cells, dendritic cells, and keratinocytes with subsequent release of a variety of cytokines and other soluble mediators. These chemical signals are responsible for keratinocyte hyperproliferation manifesting as characteristic scaly plaques, and they also contribute to the augmented inflammation underlying a number of systemic disease associations, including metabolic syndrome, cardiovascular disease, and psoriatic arthritis. To inhibit the inflammation underpinning this condition, a number of topical and systemic medications have been created with varying success. Topical treatments refer to agents that are applied directly on the skin in order to exert their therapeutic action. AM is a group of diverse medical and health care practices and products that are not presently considered to be part of conventional medicine.

2133 These therapies can be defined as alternative when are used in place of conventional

2134 treatments and complementary when used together with conventional treatments.