ISSN: 1545 9616

October 2026 • Volume 25 • Issue 10

JOURNAL OF DRUGS IN DERMATOLOGY

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Journal of Drugs in Dermatology (JDD)
is indexed in MEDLINE®/PubMed® and is published monthly by the
***SanovaWorks*, c/o WebMD**
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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

The Essential Role of Topical Targeted Therapy in Atopic Dermatitis

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ABSTRACT

Background: Atopic dermatitis (AD) is a chronic inflammatory skin disorder marked by immune dysregulation, epidermal barrier dysfunction, microbiome imbalance, pruritus, and xerosis. Despite therapeutic advances, topical treatments remain the foundation of AD management across all severities. However, most existing topicals address only limited aspects of the disease such as itch or inflammation, resulting in frequent relapse and patient dissatisfaction.

Methods: A focused literature review of topical AD therapies published between January 2015 and July 2025 was conducted, emphasizing efficacy and safety. Recent findings were synthesized in this narrative review to highlight the ongoing role of topical treatments in AD management.

Results: AD is a multifactorial condition influenced by *Staphylococcus aureus* colonization, immune dysregulation, genetic susceptibility, and environmental factors. These contribute to disease pathogenesis, the itch-scratch cycle, and barrier disruption. While systemic therapies are important, AD treatment continues to rely heavily on topical agents. Optimal management should target inflammation, restore barrier function, and address microbiome dysbiosis. Most current treatments focus on individual disease components, with few addressing the full pathogenic spectrum. Emerging evidence on zabalafin (9.5%) hydrogel, a novel botanical topical therapy, suggests potential multi-target benefits, including anti-inflammatory, antipruritic, antimicrobial, and anti-xerotic effects.

Conclusion: There remains a significant unmet need for topical therapies that comprehensively address the AD continuum, including inflammation, itch, barrier dysfunction, and microbial imbalance. Novel agents such as zabalafin may help bridge this gap.

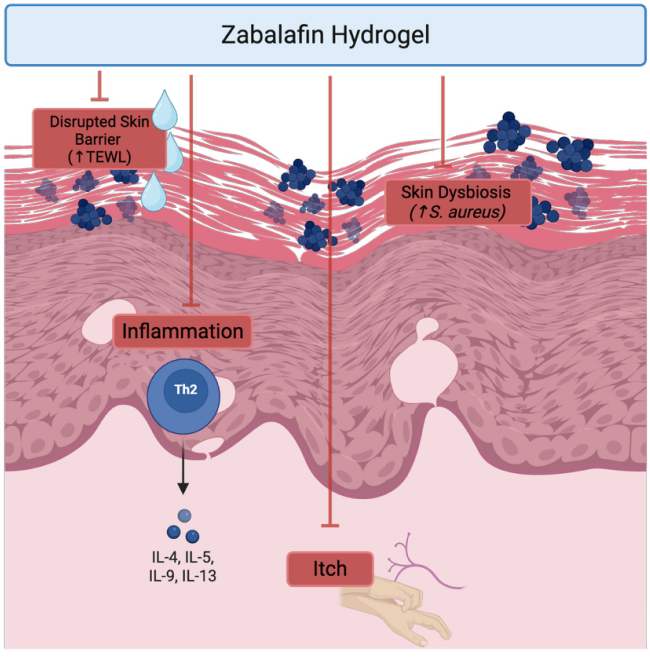
J Drugs Dermatol. 2026;25(10):898-902. doi:10.36849/JDD.10052

INTRODUCTION

Atopic dermatitis (AD) is a common inflammatory skin disease with a relapsing and remitting course over a patient's lifetime.[1,2] This chronic skin condition is estimated to affect up to 20% of children and 1% to 6% of adults worldwide.[3] AD is a heavily heterogeneous spectrum of disease affecting all age groups and skin types with varied clinical presentation and severity. The disease exists on a continuum with 4 significant skin findings: inflammation, dysbiosis/colonization/infection, pruritus, and xerosis, termed the "4 demons".[4]

Clinically, AD presents with recurrent, erythematous, pruritic eczematous plaques accompanied by dry, sensitive skin. AD frequently begins in infancy or early childhood and affects over 30 million people in the United States. The prevalence of this widespread disease is associated with an estimated global economic cost of $5 billion annually.[5] In addition, AD is associated with increased stress, low self-esteem, poor sleep, and overall decreased quality of life.[6]

FIGURE 1. Zabalafin hydrogel mechanism of action.



Zabalafin targets all aspects of the atopic dermatitis continuum by addressing skin dysbiosis, inflammatory dysregulation, xerosis, and itch.

AD has a complex pathophysiology involving immune dysregulation, genetic predisposition, environmental factors, *Staphylococcus aureus* colonization, and skin dysbiosis, all of which contribute to intense pruritus and a compromised skin barrier.[4] There has been extensive scientific debate regarding whether AD is primarily driven by epidermal barrier dysfunction ("outside-in") leading to antigen penetration and subsequent immune activation, or by inherent immune dysregulation ("inside-out"), in which aberrant T helper cell (Th) 2 cell activation results in barrier dysfunction and disease progression.[4] Regardless of the inciting factor, successful treatment should target as many pathogenic factors as possible.

This treatment paradigm starts with topical therapies that provide local, skin-specific therapy while offering symptomatic relief.[7] Topical therapy is the essential foundation of AD disease management. Topicals treat the disease directly at the site and provide patients with rapid symptomatic relief. Currently available topicals may be divided into 4 categories: (1) moisturizers and emollients, (2) topical corticosteroids (TCS), (3) topical calcineurin inhibitors (TCI), and (4) topical nonsteroidal agents such as PDE4 inhibitors (crisaborole, roflumilast), JAK inhibitors (delgocitinib [only approved for hand eczema], ruxolitinib), and aryl hydrocarbon receptor agonist (tapinarof).[6] Most of these agents target the diseased skin barrier by reducing inflammation and helping restore skin hydration; however, none addresses all 4 aspects of AD pathology: inflammation, *S. aureus* bacteria, pruritus, and xerosis.[8]

Here, we present evidence from a literature review highlighting the critical role of topical therapies in addressing the AD disease trajectory. We also introduce zabalafin hydrogel, a novel botanical topical treatment that addresses all aspects of AD pathogenesis, unlike any existing singular topical agent.

MATERIALS AND METHODS

Literature Review

The authors reviewed the most recent literature on the efficacy and safety profiles of topical therapy for maintaining control of the AD continuum, focusing on 3 main topics: (1) place in therapy of topicals (2) effectiveness and safety of topicals, and (3) different approaches to the management of patients treated with topicals in a real-world clinical setting.

Two authors (AA and SG) conducted a structured literature review on AD triggers and current best practices in topical AD treatment, searching PubMed and Google Scholar with the following search terms: *AD triggers AND skin dysbiosis OR staphylococcus aureus-driven colonization OR infection OR immunological OR genetic OR environmental OR inflammation.*

AD flares AND topical treatment OR topical corticosteroids OR topical calcineurin inhibitors OR PDE-4 I OR Zabalafin OR topical antimicrobial OR antimicrobial resistance OR topical antibiotic OR topical antibiotic resistance OR cyclosporine OR interleukin (IL)-4/13 inhibitors OR IL-13 inhibitors OR JAK inhibitors.

Excluded were publications in languages other than English, not including topicals for AD. The review process involved examining titles and abstracts, followed by full articles. Selected articles included clinical guidelines, algorithms, consensus papers, systematic literature reviews, and clinical studies published in English from January 2015 to July 2025. Selected publications were manually reviewed, with any discrepancies resolved through discussion. This process yielded 34 articles that qualified for inclusion and were deemed clinically relevant to inform the crucial role of topical treatment for the AD continuum.

SAIGE (*S. aureus*, Immune Dysregulation, Genetic Predisposition, Environmental Influence) Triggers

The pathogenesis of AD is multifactorial and driven by complex interactions among triggers, including *S. aureus* colonization and infection, immune dysregulation, genetic predisposition, and environmental factors. Taken together, these triggers are termed the SAIGE triggers.[4] SAIGE triggers are uniquely intertwined and together contribute to disease onset and exacerbations. For example, skin microbiome dysbiosis and *S. aureus* overgrowth are characteristic of lesional AD skin. This dysbiosis and *S. aureus* colonization are thought to be primary drivers of inflammation, itch, and subsequent skin barrier disruption in AD.[4]

Deng et al demonstrate that *S. aureus* directly activates pruriceptor sensory neurons that drive itch and lead to the itch-scratch cycle and subsequent scratch-induced skin damage.[9] Further studies have found that other bacteria, including *Corynebacterium mastitidis* and *Corynebacterium bovis*, are present at the onset of AD. *C. bovis* was shown to be primarily responsible for driving a robust Th2 cell response, while *S. aureus* potentiated these signals to AD manifestation.[10]

Clinically, patients with mild dysbiosis may present with mild inflammation or flares, whilst those with *S. aureus* overabundance will present with moderate to severe AD. Further, the proportion of *S. aureus* has been shown to be higher during disease flares, suggesting that AD treatments that reduce *S. aureus* populations and restore skin microbial diversity would be most effective.[11] Remaining SAIGE factors, such as environmental season changes, genetic predisposition, or existing immune dysregulation, may also significantly contribute to determining in which way the *S. aureus*-driven AD pendulum will swing.[4,12]

Essential Role of Topical Therapy in Atopic Dermatitis Management

Topical therapy is the key component of real-world AD treatment. This is evidenced by pivotal AD clinical trials such as Liberty Ad Chronos, which investigated dupilumab in conjunction with TCS and TCI therapy, highlighting the essential and ubiquitous use of topical therapy in AD.[13,14] These study designs reinforce the vital role that topicals play in the management of AD regardless of concomitant systemic therapies.

Effective management of AD begins with topical therapy aimed at repairing the defective skin barrier. Moisturizers are the foundation of optimal AD treatment, regardless of disease severity. They reinforce the damaged epidermal barrier, which is associated with increased transepidermal water loss (TEWL) and enhanced penetration of foreign antigens.[15] In addition, AD-affected skin has been linked to filaggrin deficiency and reduced levels of key epidermal lipids such as ceramides, fatty acids, triglycerides, and cholesterol, which are critical for maintaining barrier integrity.[15] Consequently, moisturizers, emollients, and humectants may help restore this weakened barrier by providing exogenous lipids, lubricating the skin, reducing TEWL, and improving skin hydration.[15] Daily moisturizer use has been shown to improve AD and is postulated to prevent or delay AD onset in infants.[16,17]

For patients who are uncontrolled with gentle skincare and moisturizers alone, TCS is often considered the first-line therapy in AD. TCS functions by broadly reducing inflammation and itch in the skin. Whilst effective, TCS are not appropriate for long-term use and may harbor unwanted cutaneous and systemic side effects such as skin atrophy, hypopigmentation, telangiectasias, and hypothalamic-pituitary-adrenal (HPA) axis suppression, particularly in children or patients with a large affected body surface area (BSA).[8] In addition, there is increasing concern of TCS withdrawal syndrome among patients and parents, which is described as worsening skin inflammation upon cessation of steroid use.[6] Taken together, the adverse effect profile of TCS has made many patients cautious of their use, with an increasing number of patients becoming "steroidphobic," which ultimately leads to under-treatment and poor treatment compliance.[6]

Corticosteroid alternatives, such as topical calcineurin inhibitors, topical JAK inhibitors, topical PDE-4 inhibitors, and topical aryl-hydrocarbon receptor agonists, are increasingly used in AD treatment, harboring fewer side effects than TCS. These alternatives are more appropriate for long-term use and have been shown to reduce AD exacerbations.[6,18] Despite their effectiveness, these topical treatments primarily target the inflammatory component of itch.

Unmet Need for Topicals in Atopic Dermatitis + Zabalafin Hydrogel

While significant advancements have been made in the field of AD, there remains a critical unmet therapeutic need for a topical therapy that targets the 4 main components of AD pathogenesis. Topicals play an overwhelmingly large role in the treatment landscape of AD. In an online survey of 2,005 patients, topical therapies were the most frequently reported modality of treatment: 85% of participants reported topical use, and 46% reported prescription topical medications.[19] Over 80% of survey participants reported having used or currently using an over-the-counter (OTC) topical, and 76% of survey participants reported having used or currently using a prescription topical. This highlights the widespread prevalence of topical therapy use and how vital it is for AD therapy.

Interestingly, despite this high rate of topical use, most patients reported high dissatisfaction with current topical therapies.[19] Thus, there exists a significant unmet need for an effective and safe topical AD agent that treats the entire AD disease continuum via a direct, multi-target approach to increase patients' response and satisfaction.

Zabalafin hydrogel is a novel, first-in-class topical agent with anti-inflammatory, anti-pruritic, anti-xerosis, and *S. aureus* modulating effects for the treatment of AD.[20] Zabalafin hydrogel is a topical botanical drug containing multiple bioactive compounds that target all aspects of the AD continuum. Application of the hydrogel forms a "liquid bandage" over the AD lesion, mimicking the effect of localized wet wraps on the skin. The zabalafin hydrogel barrier helps to restore microbiome balance and skin barrier function.

A randomized, double-blind, vehicle-controlled phase 2a clinical trial evaluated the safety and efficacy of zabalafin (9.5%) hydrogel in treating AD in adults and children with AD aged >2 years (n=41) over a 4-week period. The hydrogel was applied twice daily in patients with mild to moderate AD without secondary infection, as well as in those with mild to moderate AD and secondary infection.[20] By week 4, over 50% of study participants achieved an EASI 75, demonstrating that the novel topical was effective in treating the inflammatory component of AD.[21] In addition, in an open-label study in infected AD patients, zabalafin hydrogel was effective in treating the bacterial component of AD, demonstrating a significant reduction in bacterial infection and colonization over a 12-week period, as well as reducing or clearing the AD.[20,21] In patients with *S. aureus* infection, 84% cleared at weeks 8 or 12, with 100% of patients with MRSA being cleared. This demonstrates the potential of zabalafin to reduce *S. aureus* levels, which, in turn, can potentially modify the disease trajectory by decreasing AD flares, which are known to be preceded by a rise in *S. aureus* levels.[11] Lastly, zabalafin was effective in treating itch, with 80% of patients achieving an NRS improvement of >4 at week 8 week and 100% reporting improved quality of life.[21] Zabalafin hydrogel has a favorable safety profile with no significant safety signals observed; only one patient during the phase 2a trials had mild transient stinging at the application site, which did not interrupt treatment.[20]

Results demonstrate that zabalafin hydrogel effectively targets AD inflammation and itch while conferring antimicrobial properties. With concerns of growing antibacterial resistance, zabalafin offers a botanical alternative with broad-spectrum antibacterial activity, with little potential for antibacterial resistance, and good activity against MRSA.[12] To summarize, zabalafin hydrogel is a comprehensive, effective, and safe topical agent that addresses the full spectrum of the AD continuum in a wide variety of AD patient ages and presentations.[20] Zabalafin disrupts bacterial replication, inhibits the AD inflammatory cascade, and attenuates pruritic mechanisms while moisturizing the skin and restoring the skin barrier, and reduces *S. aureus* levels (Figure 1).[12]

Topical Therapy in an Eczema Action Plan

The mainstay of therapy for all AD patients is topicals. Topicals are constantly used at all stages of AD, from mild to severe, and should be used in combination with systemic agents to help patients get clear and stay clear from AD.[6] These topical agents can become especially helpful when addressing flares while on systemic options, as they work rapidly to relieve patients of their symptoms. Many patients and physicians will partner to develop personalized eczema action plans for potential flares. These plans typically include the use of a TCS, moisturizer, and gentle cleanser for up to one week to treat flares. A maintenance regimen of topical non-steroidal may follow this to maintain AD "hot spots" clear, accompanied by moisturizers and a gentle cleanser.[6]

However, the drawback to the topicals proposed in this plan is that TCS and most non-steroidal topicals only address the inflammatory aspect of the AD continuum. Ideally, a topical would address all aspects of AD pathogenesis to help achieve and maintain control of AD flares. Zabalafin hydrogel targets all 4 AD demons and provides the antimicrobial activity required to break the cycle of *S. aureus*-triggered AD flares. As a safe, gentle, and pain-free efficacious botanical product, zabalafin does not harbor the unfavorable side effect profile of TCS, which may make it more appealing to steroid-phobic individuals or for the pediatric population. Taken together, zabalafin is an essential addition to the topical AD armamentarium as it is the only topical to date that targets all aspects of the AD continuum effectively and safely.

CONCLUSION

Topical therapy is an essential pillar of AD treatment and management. Most AD patients will use a topical treatment at some point in their lifetime. Therefore, effective and safe topicals for the greater AD-affected population are vital. AD is a complex, highly heterogeneous disease that is largely understood to be triggered and exacerbated by SAIGE factors. To date, most topical and systemic therapies have primarily focused on immune dysregulation associated with AD flares. Currently available topicals, such as TCS, address AD inflammation but do not directly address skin microbiome dysbiosis and xerosis. Zabalafin (9.5%) hydrogel was found to be the only topical that synchronously addresses the full spectrum of the AD continuum at the skin. In addition, the botanical anti-microbial activity of the novel topical introduces disease-modifying potential by reducing pathogenic *S. aureus*, including MRSA, population in the skin microbiome.

DISCLOSURES

An educational grant from Alphyn Biologics, Inc., Cincinnati, OH, supported the research for this work. The authors (PL, AAH, SG, PK, MEG, LAS) participated in designing the research for this work and in finalizing the manuscript for publication; all agreed with the final content. All authors (PL, AAH, SG, PK, MEG, LAS) read and approved the final version of the manuscript and its publication.

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doi:10.36849/JDD.10402

October 2026 903 Volume 25 • Issue 10

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Injectable NASHA Gel Skinbooster for Facial Skin Aging in Premenopausal and Postmenopausal Women With Estrogen Deficiency-Associated Not Receiving Hormone Therapy: A Case Series

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ABSTRACT

Background: Estrogen deficiency contributes substantially to intrinsic skin aging by reducing dermal collagen, impairing hydration, decreasing elasticity, and compromising overall skin quality. Although hormone therapy may attenuate these changes, many are either unwilling or unable to receive systemic hormonal treatment. Injectable nonanimal stabilized hyaluronic acid (NASHA) gel skinboosters may represent a nonhormonal approach for improving skin quality in this population.

Objective: To evaluate the efficacy of an infiltrative treatment of injectable hyaluronic acid NASHA gel skinbooster antiaging treatment to improve and restore skin quality in premenopausal and postmenopausal women with estrogen deficiency–associated skin aging who were not receiving hormone therapy.

Methods: This prospective observational case series included 10 women (5 premenopausal and 5 postmenopausal) with mild-to-moderate climacteric symptoms and no history of hormone therapy. All participants underwent gynecologic-hormonal and dermatologic evaluation before receiving 3 monthly treatment sessions with injectable NASHA gel skinbooster. Clinical assessments, standardized photography, and patient-reported outcomes were obtained at baseline(T0), after 3 monthly treatments (T1), after 4 months (T2), and after 6 months (T3).

Results: Participants demonstrated clinical improvement in multiple parameters of facial skin quality following treatment. Improvements were observed in hydration, texture, elasticity, and the appearance of fine lines and roughness. Standardized photographs showed progressive aesthetic improvement throughout follow-up, and patients reported high levels of treatment satisfaction. The treatment protocol was well tolerated, with only minor transient injection-related reactions.

Conclusions: In this case series, treatment with injectable NASHA gel skinbooster was associated with improvements in facial skin quality in women with estrogen deficiency who were not receiving hormone therapy. These findings suggest that injectable NASHA gel skinbooster may represent a useful adjunctive nonhormonal approach for improving visible manifestations of estrogen-deficiency-related facial skin aging.

J Drugs Dermatol. 2026;25(10):903-908. doi:10.36849/JDD.10402

INTRODUCTION

Menopause is a physiological stage in a woman's life characterized by the permanent cessation of ovarian follicular activity and a consequent decline in circulating estrogen levels. This transition reflects a complex neuroendocrine remodeling of the hypothalamic-pituitary-ovarian (HPO) axis and results in systemic changes that extend far beyond reproductive function. Estrogen deficiency affects multiple organ systems, including the cardiovascular, metabolic, skeletal, genitourinary, immune, and integumentary systems, contributing to a broad range of clinical manifestations that may significantly influence both overall health and quality of life.[1–3]

Neuroendocrine and Hormonal Changes

The menopausal transition is characterized by a progressive decline in ovarian reserve, reflected by decreasing anti-Müllerian hormone (AMH) and inhibin B concentrations. The resulting reduction in negative feedback to the hypothalamus and pituitary gland leads to increased secretion of gonadotropins, particularly follicle-stimulating hormone (FSH), often exceeding 25–30 IU/L, and increased luteinizing hormone (LH) levels.[4]

Estradiol (E2), the predominant biologically active estrogen during the reproductive years, declines substantially throughout the menopausal transition and frequently reaches serum concentrations below 20 pg/mL after menopause. Estrone

(E1), produced primarily through peripheral aromatization of androstenedione in adipose tissue, becomes the predominant circulating estrogen, although it possesses lower receptor affinity and reduced biological activity than estradiol.

In addition, a relative hyperandrogenic state may develop as circulating estrogen concentrations decline more rapidly than adrenal and ovarian androgen production. The changing hormonal milieu has implications for the skin, where the balance of estrogenic and androgenic signaling influences sebaceous activity, hair growth, epidermal function, and dermal homeostasis.

Definition of Premenopausal and Postmenopausal Status

For the purposes of this study, premenopausal women were defined as those with regular or mildly irregular menstrual cycles, preserved ovarian function, and circulating estradiol concentrations within the reproductive range. Hormonal patterns during this stage are characterized by cyclic fluctuations in estradiol (E2) and progesterone, with follicle-stimulating hormone (FSH) levels generally remaining within the expected range for reproductive-aged women.

Postmenopausal women were defined according to established clinical criteria as those who had experienced the permanent cessation of menstruation for at least 12 consecutive months, accompanied by ovarian follicular depletion and a persistent hypoestrogenic state. This condition is hormonally characterized by low circulating estradiol concentrations (generally <20 pg/mL) together with elevated gonadotropin levels, particularly FSH concentrations typically exceeding 25–30 IU/L.

In all participants, menopausal status was determined by a specialist in gynecology based on clinical history, menstrual pattern, and hormonal evaluation when clinically indicated, in accordance with current clinical practice.

Estrogen Deficiency as a Systemic and Cutaneous Process

The decline in estrogen concentrations during menopause produces widespread physiological effects throughout the body. Taken together, these systemic changes underscore that the menopausal transition represents a broader physiologic response to declining estrogen rather than an isolated reproductive event. For dermatologists, this context is particularly relevant because changes in the skin may be among the most visible manifestations of this altered hormonal environment. Facial aging during the menopausal transition therefore reflects not only chronological aging and cumulative environmental exposure, but also changes associated with declining estrogen signaling.

Central Nervous System and Thermoregulation

Estrogens regulate multiple neurotransmitter systems, including serotonergic and noradrenergic pathways, and play an essential role in hypothalamic thermoregulation. Consequently, declining estrogen levels contribute to vasomotor symptoms, including hot flashes and night sweats, which affect up to 75% of menopausal women.

Cardiovascular System

Estrogen exerts important vasoprotective effects by enhancing nitric oxide production, reducing vascular inflammation, and improving lipid metabolism. Following menopause, estrogen deficiency is associated with increased low-density lipoprotein (LDL) cholesterol, reduced high-density lipoprotein (HDL) cholesterol, endothelial dysfunction, and an overall increase in cardiovascular risk.

Metabolic Changes

Estrogen deficiency promotes insulin resistance and central adiposity, resulting in preferential visceral fat accumulation. These metabolic alterations contribute to the development of metabolic syndrome and chronic low-grade inflammation, commonly referred to as *inflammaging*.[5]

Skeletal System

Estrogens inhibit osteoclast-mediated bone resorption. Their decline accelerates bone turnover, reduces bone mineral density, and increases the risk of osteoporosis and fragility fractures.

Immune System and Inflammation

Menopause has been associated with alterations in systemic pro-inflammatory cytokine activity, including IL-6 and TNF-α, although the magnitude and consistency of these changes across studies remain heterogeneous, contributing to chronic inflammation and progressive tissue degeneration.[6]

Genitourinary System

The hypoestrogenic state also contributes to the development of the genitourinary syndrome of menopause (GSM), characterized by vulvovaginal atrophy, vaginal dryness, urinary symptoms, and alterations in the vaginal microbiome.[7]

Skin as a Target Organ of Estrogen Deficiency

The skin is a hormonally responsive organ that expresses both estrogen receptor alpha (ER-α) and estrogen receptor beta (ER-β) in keratinocytes, fibroblasts, sebaceous glands, and other cutaneous structures. Through these receptors, estrogens play an essential role in maintaining skin homeostasis by regulating collagen synthesis, dermal thickness, hydration, glycosaminoglycan production, sebaceous gland activity, wound healing, and overall skin integrity. Estrogen signaling is therefore critical for preserving both the structural and functional characteristics of healthy skin.

The decline in estrogen levels associated with menopause results in progressive deterioration of skin structure and

function. One of the earliest and most significant changes is the rapid loss of dermal collagen, with studies demonstrating that up to 30% of collagen may be lost during the first 5 years after menopause. This reduction contributes to thinning of the dermis, decreased elasticity, and diminished mechanical strength, changes that are particularly evident in the face, where skin aging has a major aesthetic impact.[8-10]

In addition to collagen loss, estrogen deficiency impairs epidermal barrier function and reduces the synthesis of glycosaminoglycans, leading to decreased hydration and increased transepidermal water loss (TEWL). As a result, the skin becomes progressively drier, rougher, and less resilient. Epidermal turnover also declines, contributing to reduced skin thickness, diminished elasticity and tone, increased laxity, and more pronounced fine lines and wrinkles. Skin texture becomes less uniform, while loss of radiance and increased dullness further accentuates the visible manifestations of facial aging.[10]

Oxidative stress also plays an important role in estrogen deficiency–associated skin aging. Increased production of reactive oxygen species, together with reduced endogenous antioxidant defenses, promotes cellular damage and accelerates the degradation of the extracellular matrix. At the same time, matrix metalloproteinases (MMPs) are upregulated, leading to increased collagen degradation, while fibroblast activity progressively declines, resulting in reduced collagen and elastin synthesis.[11] Collectively, these mechanisms contribute to the structural changes that characterize intrinsic skin aging during the menopausal transition.

These changes suggest that menopausal skin may represent a distinct biologic treatment environment. In contrast to chronological and photoaging alone, estrogen deficiency affects several components of skin quality simultaneously, including collagen homeostasis, extracellular matrix composition, hydration, elasticity, and dermal thickness. Recognition of this hormonally influenced component of facial aging may therefore be relevant when selecting treatments designed to improve skin quality rather than primarily restore volume or alter facial contours.

Rationale for Injectable Treatment With Hyaluronic Acid NASHA Skinbooster

Although hormone therapy has been shown to improve several manifestations of estrogen-deficiency–related skin aging, many women either decline systemic hormone therapy or have medical contraindications to its use. Consequently, there is growing interest in nonhormonal approaches that improve skin quality while avoiding systemic hormonal exposure.

Injectable nonanimal stabilized hyaluronic acid (NASHA) gel skinboosters have been developed to improve skin quality by restoring hydration and enhancing dermal function rather than creating facial volume. In addition to providing deep dermal hydration, experimental and clinical studies suggest that hyaluronic acid may stimulate fibroblast activity, promote collagen synthesis, improve dermal elasticity, and enhance overall skin quality. These biological effects may help counteract some of the cutaneous manifestations associated with estrogen deficiency.[12,13]

Based on these observations, injectable NASHA gel skinbooster treatment may represent a valuable adjunctive, nonhormonal strategy for improving facial skin quality in women experiencing estrogen deficiency who are not receiving hormone therapy.

The objective of the present prospective case series was to evaluate the clinical effects of injectable NASHA gel skinbooster treatment on facial skin quality in premenopausal and postmenopausal women with estrogen deficiency who were not undergoing hormone therapy.

MATERIALS AND METHODS

Study Design

This prospective observational case series was conducted to evaluate the effects of injectable nonanimal stabilized hyaluronic acid (NASHA) gel skinbooster treatment on facial skin quality in women with estrogen deficiency–associated facial skin aging who were not receiving hormone therapy.

Study Population

Ten women were enrolled in the study and stratified according to menopausal status. Group A consisted of 5 premenopausal women between 44 and 46 years of age, and Group B consisted of 5 postmenopausal women between 53 and 55 years of age. All participants underwent comprehensive gynecologic and dermatologic evaluation before enrollment.

Eligible participants were women 40 to 60 years of age who presented with mild-to-moderate climacteric symptoms, had no current or previous history of hormone therapy, demonstrated moderate facial skin aging corresponding to Grade 2 on the Galderma Facial Assessment Scale (FAS) and Grade II on the Glogau Photoaging Classification, had no history of autoimmune disease, and provided written informed consent before participation.

Standardized Full-Face Infiltrative Treatment Protocol

All patients underwent a standardized full-face infiltrative treatment protocol using injectable nonanimal stabilized hyaluronic acid (NASHA) gel with lidocaine (Restylane® Skinboosters™ Vital Lidocaine, 20 mg/mL; Q-Med AB, Galderma, Uppsala, Sweden).

Treatment consisted of 3 sessions performed at monthly intervals. Patients with moderate facial skin aging received 1 mL of product per session. Patients with more severe facial skin aging received 2 mL of product per session.

The product was administered using the proprietary Smart Click Syringe, which enables precise delivery of 10-µL drops, typically totaling approximately 100 drops during each treatment session. Injections were performed using a 29-gauge needle with a retrograde injection technique into the deep dermis or superficial subdermis.

The standardized full-face infiltrative treatment protocol primarily targeted the midface and jawline. Particular attention was paid to maintaining the appropriate depth of injection. Product should not be injected too superficially, as this may result in the formation of visible or palpable micro-papules. When the technique is performed correctly, no visible or palpable bumps should remain following treatment.

Minor bruising may occur after treatment but generally resolves spontaneously within several days. Patients were advised to avoid direct sun exposure for approximately 1 week following each treatment session.

Outcome Measures

Treatment efficacy was evaluated using investigator-based clinical assessment, standardized digital photography, and patient-reported outcomes.

Clinical assessment included the Galderma Facial Assessment Scale (FAS), as described by Jain et al, and the Glogau Photoaging Classification.14 The FAS is a validated 4-point grading scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe) used to assess static and dynamic wrinkles and overall facial skin quality. The Glogau Photoaging Classification was used to evaluate the severity of facial photoaging.

Standardized digital photographs were obtained using a Nikon D5300 digital single-lens reflex camera equipped with an 18–140-mm lens. Patient-reported outcomes were collected throughout the study to assess participants' perceptions of treatment response and overall satisfaction.

Follow-up

Patients were evaluated at baseline (T0), after completion of 3 monthly treatment sessions (T1), after 4 months (T2), and after 6 months (T3). At each evaluation, clinical assessment using the Galderma Facial Assessment Scale and the Glogau Photoaging Classification was performed, standardized digital photographs were obtained, and patient-reported outcomes were recorded to assess treatment response over time.

RESULTS

Ten women completed the study, including 5 premenopausal and five postmenopausal participants. All patients completed the 3-session treatment protocol with Restylane® Skinboosters™ Vital Lidocaine and attended the scheduled follow-up evaluations.

Clinical improvement in facial skin quality was observed following treatment in both the premenopausal and postmenopausal groups following treatment. Improvements in skin hydration,

FIGURE 1. Clinical photographs of postmenopausal participants treated with Restylane® Skinboosters™ Vital Lidocaine (20 mg/mL; Galderma) using the standardized full-face infiltrative treatment protocol. Images obtained at baseline (T0), after completion of the 3 monthly treatment sessions (T1), after 4 months (T2), and after 6 months (T3) follow-up illustrate the progressive improvements in facial skin quality observed during the study.



FIGURE 2. Clinical photographs of premenopausal participants treated with Restalyne® Skinboosters™ Vital Lidocaine (20 mg/mL; Galderma) using the standardized full-face infiltrative treatment protocol. Images obtained at baseline (T0), after completion of the 3 monthly treatment sessions (T1), after 4 months (T2), and after 6 months (T3) follow-up illustrate the progressive improvements in facial skin quality observed during the study.



elasticity, and overall skin appearance were documented by investigator assessment, with corresponding improvements using the Galderma Facial Assessment Scale (FAS) and the Glogau Photoaging Classification. Standardized digital photography demonstrated visible improvements in facial skin quality over the course of treatment (Figures 1 and 2).

Patient-reported outcomes were consistent with the clinical findings, with participants reporting improvement in overall skin quality and satisfaction with treatment. The treatment protocol was well tolerated. Minor bruising occurred occasionally following injection and resolved spontaneously without intervention. No persistent visible or palpable irregularities were observed when the standardized injection technique was used.

DISCUSSION

Estrogen deprivation represents a major driver of intrinsic skin aging, affecting multiple organ systems, including the skin. In the absence of systemic hormone therapy, dermatologic interventions may play an important role in mitigating the visible effects of estrogen deficiency. In this prospective case series, treatment with injectable nonanimal stabilized hyaluronic acid (NASHA) gel as a skinbooster using a standardized full-face infiltrative treatment protocol was associated with improvements in skin quality and favorable patient-reported outcomes. These observations suggest that this minimally invasive approach may represent an effective nonhormonal option for improving the appearance and quality of facial skin in women experiencing estrogen deficiency.

The present case series is of particular interest because treatment was evaluated in women who were not receiving hormone therapy, allowing changes in skin quality to be considered in the setting of the underlying menopausal hormonal environment without concurrent systemic hormonal treatment. Rather than addressing facial volume loss alone, the treatment approach was directed toward skin quality, including hydration, texture, elasticity, fine lines, and roughness—features that may be particularly affected during the menopausal transition.

Restylane® Skinboosters™ Vital Lidocaine (20 mg/mL; Galderma) is designed to improve skin quality through deep dermal hydration while supporting fibroblast activity and new collagen synthesis. Previous clinical studies demonstrated that NASHA skinboosters improve 6 key aspects of skin quality, including surface uniformity through reduced visibility of enlarged pores; smoothness, by reducing roughness and improving skin texture; uniformity of skin tone, with improvement in pigmentation and age spots; improvement in fine lines and wrinkles, through enhanced elasticity; glow, by restoring deep hydration and skin radiance; and scars, particularly atrophic acne scars. These recognized treatment benefits are consistent with the clinical observations in the present case series and support the role of injectable NASHA gel as a treatment for estrogen deficiency-associated facial skin aging.[15–28]

Rather than restoring facial volume, treatment is intended to improve the overall quality of the skin by enhancing hydration, elasticity, texture, and radiance. In the present study, the standardized full-face infiltrative treatment protocol was well

tolerated and produced progressive clinical improvement throughout the follow-up period.

The patient-reported outcomes observed in this study further support the clinical findings. Participants regarded the treatment favorably and expressed satisfaction with the improvements in skin quality achieved with this minimally invasive protocol. The treatment was associated with minimal downtime and was well tolerated, making it a practical option for women seeking improvement in facial skin quality without systemic hormone therapy. Preliminary observations also suggested progressive and sustained aesthetic improvement over the course of follow-up.

In addition to the visible improvements in skin quality, participants reported enhanced psychological well-being, including increased self-esteem, greater self-confidence, and improved satisfaction with their appearance. Although these observations were based on patient-reported outcomes, they highlight the broader impact that improvement in skin quality may have on overall well-being in women experiencing estrogen deficiency–associated facial aging.

CONCLUSION

Estrogen deficiency is associated with progressive deterioration in facial skin quality, resulting in reduced hydration, elasticity, and dermal support, with the subsequent development of visible signs of skin aging. For women who are not candidates for or who choose not to undergo hormone therapy, effective nonhormonal treatment options are needed to address these changes.

In this prospective case series, a standardized full-face infiltrative treatment protocol using injectable nonanimal stabilized hyaluronic acid (NASHA) gel as a skinbooster (Restylane® Skinboosters™ Vital Lidocaine, 20 mg/mL; Galderma) was associated with improvements in clinical skin quality, favorable patient-reported outcomes, and high treatment tolerability. The protocol was minimally invasive, well tolerated, and designed to restore skin hydration, texture, elasticity, and skin radiance ("glow") while preserving natural facial contours without creating additional volume.

These observations support the use of injectable NASHA gel as a valuable adjunctive, nonhormonal approach for restoring skin quality and achieving natural-looking facial rejuvenation in both premenopausal and postmenopausal women.

DISCLOSURES

No funding or sponsorship was received for the conduct of this study or the publication of this article.

The authors report no conflicts of interest relevant to this work.

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doi:10.36849/JDD.9771

October 2026 909 Volume 25 • Issue 10

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Biopsy Type and Metastatic Recurrence in Melanoma: A Cohort Study

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ABSTRACT

Background: Melanoma is a dynamic health problem caused by deteriorating melanocytes that generate aberrant melanin that gives color to the skin. It remains the leading cause of death from skin cancer. The incidence and mortality rates of melanoma emphasize the need for a suitable diagnostic biopsy, which is important for the optimal treatment of newly observed melanoma patients.
Objectives: This study aims to evaluate the presence of melanoma metastases, mitotic rate, ulceration, and Breslow thickness, which are the most significant predictors of mortality from melanoma and are important for the diagnosis and optimal treatment of newly diagnosed melanoma patients.
Methods: A cohort of 56 patients diagnosed with melanoma in the upper or lower limbs between 2020 and 2024 was analyzed to investigate whether partial biopsies influence melanoma metastasis. All patients underwent biopsy followed by complete resection and were followed for 3 years. We evaluated clinical characteristics, including Breslow thickness, surgical excision width, CLARK grade, ulcer presence, vascular invasion, and biopsy-excision interval, for their influence on recurrence time. The relationships between these factors and recurrence were assessed using the rank sum test and Spearman correlation analysis.
Results: The results revealed that all patients had metastasis at varying intervals post-surgery, with different patterns observed between upper and lower limb melanomas. However, the correlation between recurrence duration and the analyzed characteristics was not statistically significant.
Conclusion: Thus, our current revelations conclude that complete resection of the tumor lesions is sufficient for patients diagnosed with melanoma after biopsy, and extended resection is unnecessary.

J Drugs Dermatol. 2026;25(10):909-912. doi:10.36849/JDD.9771

INTRODUCTION

Melanoma is a serious form of skin cancer caused by deteriorating melanocytes that generate aberrant melanin, the pigment that gives skin its color. It remains the leading cause of death from skin cancer and is expected to rise globally in the upcoming years.[1,2] Tumor features such as the presence of metastases, mitotic rate, ulceration, and Breslow thickness are the most significant predictors of mortality from melanoma.[2] The incidence and mortality rates of melanoma emphasize the need for a suitable diagnostic biopsy, which is important for the optimal treatment of newly observed melanoma patients. In parallel, the tumor characteristics of the initial melanoma provide physicians with crucial prognostic and staging information, as well as guidance for treatment.[3,4]

The selection of a particular biopsy approach has been found to depend on the size and location of the pigmented lesion, as well as the observations and experience of the physician (Sharma et al). In terms of surgical care, guidelines recommend performing a

diagnostic excision biopsy (DEB) no later than 2 weeks after the patient first presents.[5,6] When treating clinically suspected melanoma, an excisional biopsy with narrow margins (2 mm) is considered an effective initial treatment. Parallel to this, partial biopsies (punch, shave, curette, and incisional biopsies) are frequently used instead of excisional biopsies.[3,7,8] However, the impact of an incisional biopsy on the prognosis for the initial diagnosis of melanoma remains debatable. It has been proposed that insufficient removal of the melanoma could cause malignant cells to be dislodged.[2,9] For this reason, some surgeons prefer complete excisions to prevent tumor cell seeding and to achieve superior histologic results.[10]

Nevertheless, shave biopsies, rather than excisional biopsies, are typically used to diagnose melanoma.[3] Whether slicing into the tumor causes injury or not remains a major concern that both doctors and patients should discuss.[10,11] Thus, considering the consequences and queries raised in the literature, our investigations aim to explore whether biopsy affects metastasis and recurrence, as well as the relationship between resection-biopsy interval, tumor mitotic rate, and ulceration.

MATERIALS AND METHODS

Between 2020 and 2024, 56 patients were initially diagnosed via biopsy and subsequently underwent complete resection of melanoma in the upper or lower extremities at our hospital. The cohort included 27 females (48.2%) and 29 males (51.8%) with a median age of 67 years, ranging from 31 to 84 years, and a mean age of 60.24 years. Patients were followed up for 3 years, with follow-up ending upon the appearance of metastases. All patients underwent CT or MRI examinations prior to complete resection.

The patients were analyzed based on Breslow thickness (Group 1. ≤1.00 mm, Group 2. 1.01–2.00 mm, Group 3. 2.01–4.00 mm, Group 4. >4.01 mm), Clark level (I–V), vascular invasion, split index, ulceration, surgical excision breadth, and biopsy-excision interval (days) vs transfer interval time (weeks).

The collected data were analyzed statistically to explore the relationships between various characteristics (Thickness, Clark level, vascular invasion, split index, ulceration, surgical excision breadth, biopsy-excision interval, and treatments) and recurrence duration using Spearman correlation analysis and rank sum tests, employing SPSS 11.5 (Statistical Package for the Social Sciences, Windows 2000, Chicago, IL).

TABLE 1.

Tumor Features of 56 Melanoma Cases		
Recorded Features	**Variables**	**n (%)**
Sex	Female	27/56 (48%)
	Male	29/56 (52%)
Age (Years)	Mean	60.24
	Median	67
	Range	31-84
Tumor anatomic site	Hand	9/56 (16%)
	Leg	2/56 (4%)
	Feet	45/56 (80%)
Thickness (mm)	1	5/54 (9.3%)
	2	6/54 (11.1%)
	3	11/54 (20.3%)
	4	32/54 (59.3%)
CLARK rating	1	2/41 (4.9%)
	2	5/41 (12.2%)
	3	11/41 (26.8%)
	4	16/41 (39%)
	5	7/41 (17.1%)
Vessels	-ve	39/44 (88.6%)
	+ve	5/44 (11.4%)
Ulcer	-ve	40/52 (77%)
	+ve	12/52 (23%)
Split index (pieces/mm^2)	Mean	8.08
	Median	6
	Range	1-28
Surgical resection width (cm)	Mean	1.56
	Median	2
	Range	0.4-4
Biopsy-excision interval (days)	Mean	25.76
	Median	18.5
	Range	5-169
Treatments	Interferon	23/53 (43.4%)
	Chemotherapy	13/53 (24.5%)
	No Treatment	17/53 (32.1%)

RESULTS

Among the 56 patients with malignant melanoma of the upper and lower limbs, 9 cases of melanoma involved the hand, with 2 cases of lung metastasis, 6 cases of simple ipsilateral axillary lymph node metastasis, 1 case of subcutaneous transitional metastasis at the surgical site, and 2 cases of lower extremity melanoma with subcutaneous transitional metastasis. Among the 45 patients with melanoma in the foot, 16 had simple ipsilateral inguinal lymph node metastasis, 19 had distant metastasis, 7 had simple subcutaneous metastasis, and 3 had combined ipsilateral inguinal lymph node metastasis and subcutaneous metastasis (Table 1).

TABLE 2.

The Relationship Between Different Characteristics of Patients and the Duration of Recurrence Via Spearman Correlation Analysis

Characteristics	r_s value	*P* value
Thickness (mm)	0.224	0.103
CLARK Rating	-0.187	0.242
Vessels	0.123	0.433
Split Index (pieces)	0.119	0.470
Ulcer	0.015	0.915
Surgical Resection Width (cm)	0.089	0.523
BiopsyResection Interval (days)	0.024	0.866
Treatements	-0.018	0.900

Spearman Correlation Analysis

Spearman correlation analysis indicated that none of the characteristics (Thickness, Clark level, Vessels, Split Index, Ulcer, Surgical Resection Width, Biopsy-Resection Interval, and Interferon) showed a statistically significant correlation with the duration of recurrence. Negligible or weak relationships were observed between the variables and recurrence duration, as the Spearman correlation coefficients (rs) for most characteristics were close to zero (Table 2). This analysis expressed Thickness (mm) with a positive correlation to recurrence duration (rs=0.224), but this was not found statistically significant (*P*=0.103). In contrast, Clark level revealed a negative correlation with recurrence duration (rs=-0.187), but statistically, this was not found significant (*P*=0.242). A statistically nonsignificant (*P*=0.433) and weak positive correlation (rs=0.123) was observed in the case of vessels. Split index (pieces) also indicated a weak positive (rs=0.119) and nonsignificant (*P*=0.470) correlation, statistically. Ulcer demonstrated a very weak positive correlation (rs=0.015), with no statistical significance (*P*=0.915). Surgical resection width (cm) was also revealed with a weak positive (rs=0.089) and statistically nonsignificant (*P*=0.523) correlation. Biopsy to resection interval (days) displayed an extremely weak positive correlation (rs=0.024), with no statistical significance (*P*=0.866). Interferon showed a very weak negative correlation (rs=-0.018), with no statistical significance (*P*=0.900; Table 2).

The findings of Spearman correlation analysis suggest that the analyzed factors may not have a strong influence on recurrence time in the studied population.

Rank Sum Test

According to the rank sum test, none of the characteristics exhibited statistically significant differences in recurrence duration between the groups, despite variability in interquartile ranges and median values across the characteristics. Clark level and Thickness exhibited some variability across categories, but statistical results were revealed as nonsignificant. Similarly, the presence of ulcers and vessels had no significant impact on the median values. Treatments including chemotherapy, interferon, and the control group were also observed to be nonsignificant (Table 3).

DISCUSSION

The use of incisional, punch, or shave biopsies is increasing regardless of guidelines recommending excisional biopsy as the diagnostic procedure for melanoma. Excisional biopsy's frequency (10–86%) for diagnostic objectives varies widely. In addition to risks such as misdiagnosis, staging inaccuracy, and diagnostic uncertainty, the belief that partial biopsy has an adverse effect on prognosis has been disproved in different reports. There has been concern that incomplete excision of melanoma could result in local, regional, or systemic tumor dissemination.[12-14] According to NCDB reports, incisional biopsies were found to be associated with decreasing overall 5-year survival. The excisional biopsy techniques recommended in the current national guidelines correlate with NCDB reports.[15-17]

TABLE 3.

Comparison of Recurrence Duration in Patients With Different Characteristics Via Rank Sum Test

Characteristics	Categories	M (P_{25}, P_{75})	Z/H value	*P* value
Thickness (mm)	Group 1 Group 2 Group 3 Group 4	7.77 (5.40, 32.90) 21.32 (8.10, 30.52) 11.30 (2.56, 18.30) 17.53 (9.07,36.25)	4.072	0.254
CLARK Rating	Group 1 Group 2 Group 3 Group 4 Group 5	32.60 (7.26, -) 15.83 (11.32, 54.22) 15.60 (7.43, 36.37) 8.17 (4.08, 19.78) 15.23 (12.87, 25.30)	5.259	0.262
Vessels	Negative Positive	14.39 (6.78, 26.13) 19.24 (7.09, 53.75)	-0.796	0.426
Ulcer	Negative Positive	11.32 (5.81, 37.42) 15.22 (7.52, 31.05)	-0.109	0.914
Treatments	Interferon Chemotherapy Control	15.20 (7.77, 36.70) 15.83 (6.22, 23.68) 12.87 (4.82,38.99)	0.985	0.611

Therefore, complete excisions are preferred to achieve better outcomes and to avoid the risk of displacing tumor cells to other locations.

A large study found no significant differences between biopsy techniques (complete excision, shave biopsy, and incisional biopsy) regarding the incidence of sentinel lymph node metastases, disease-free survival, locoregional recurrences, overall survival, or distant disease-free survival. Some results revealed that the type of diagnostic biopsy or the tumor cells' presence in the re-excision specimen have no influence on the survival of the melanoma patient.[15,18] In terms of surgical management, the United States National Comprehensive Cancer Network and British Society of Dermatology recommended diagnostic excision biopsy within 2 weeks of initial presentation. However, there are no guidelines on the optimal time interval between a diagnostic excision biopsy and a wide local excision. Hence, the guidelines of the European Dermatology Forum suggest definitive surgical management within 4 to 6 weeks of the initial diagnosis.[19,20]

Since the biopsy method does not appear to affect progression-free survival (PFS) or overall survival (OS), we aimed to explore whether different surgical methods promote tumor metastasis and whether strict expansion surgery or even amputation is necessary after an initial local biopsy. Our statistical results suggest that all 56 patients who underwent local biopsy developed metastases after secondary expansion surgery. Only 4 patients (7.5%) had subcutaneous transitional metastases, while the others experienced metastases distant from the surgical site. Based on these findings, we believe that for patients undergoing an initial partial biopsy, expansion surgery may not provide additional benefit during subsequent surgical resection. The tumor may already be adequately removed during re-operation after the biopsy. Our analysis further suggests that melanoma metastasizes away from the surgical site 100% of the time after local excision and pathological examination. This behavior is comparable to a wasp's nest. When undisturbed, the wasps' range of activity remains relatively limited. However, once stimulated, their activity spreads irregularly and rapidly. Similarly, melanoma may already have distant metastases in the early stage, which act as "sentinels" indicating early distant dissemination. The biological behavior of melanoma after being stimulated (eg, through partial biopsy) closely resembles the behavior of wasps when provoked. We refer to this phenomenon as the "wasp effect."

Our study results suggest that expanding the scope of resection in melanoma patients after biopsy does not prevent metastasis, and complete resection of the tumor lesions can help reduce the patient's surgical pain. Future research should focus on exploring whether differences in recurrence and metastasis exist in melanoma patients who undergo extended resection and biopsy at the time of initial diagnosis, providing data to support future treatment principles.

CONCLUSION

The impact of partial biopsy on the recurrence of 56 cases of upper and lower limb melanoma after complete resection was analyzed. The rank sum test and Spearman correlation analysis showed no significant correlation between any factor and the duration of recurrence or metastasis. Although all patients experienced varying degrees of metastasis after surgery, none of the factors studied significantly influenced the duration of recurrence. The study concluded that the analyzed factors did not have a statistically significant impact on melanoma recurrence. Therefore, we believe that expanding the scope of resection after biopsy does not prevent metastasis, and complete resection of the tumor lesion is sufficient.

DISCLOSURES

The authors have no conflicts of interest to disclose.

Funding statement: Kunming Medical University Leading Research Program (Challenge-Oriented Initiative)-general program NO: QL-JBGS-13. 2. Decoding the Future -Translational Oncology NO: chmdf2025-JMWL-11-10.

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doi:10.36849/JDD.10209

October 2026 914 Volume 25 • Issue 10

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Contact Allergens Associated With Nummular Eczema: A Systematic Review

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ABSTRACT

Background: Nummular eczema (NE) is a prevalent and chronic inflammatory dermatosis marked by pruritic, coin-shaped eczematous plaques. Contact allergen sensitization may play a role in NE etiology.

Methods: On April 30, 2026, PubMed, Embase, and the Cochrane Library were searched per PRISMA guidelines for studies investigating triggers or aggravators of NE through patch testing.

Results: Of 287 studies identified, 10 observational studies met the inclusion criteria. The median overall patch test positivity among patients with NE was 47.8% (range: 26.7% to 56.0%). The most frequently reported allergens included nickel and nickel sulfate, potassium dichromate, cobalt chloride, fragrance mix, neomycin, colophony, formaldehyde, paraphenylenediamine, and rubber-related allergens. Among studies reporting concomitant allergic contact dermatitis (ACD), a median of 33.5% of patients with NE had concurrent or prior ACD.

Conclusions: Available observational evidence suggests that contact allergen positivity is common among patients with NE. Patch testing should be considered for patients with severe or treatment-refractory NE to identify clinically relevant allergens and guide trigger-avoidance strategies. Further studies using standardized patch testing protocols and assessments of clinical relevance are needed to clarify whether contact sensitization is an etiologic factor, a disease aggravator, or a comorbid finding in NE.

J Drugs Dermatol. 2026;25(10):914-918. doi:10.36849/JDD.10209

INTRODUCTION

Nummular eczema (NE) is a chronic inflammatory dermatosis marked by pruritic, coin-shaped eczematous plaques most commonly affecting the extremities and trunk.[1] NE, also referred to as discoid eczema, primarily affects middle-aged and elderly men, with a reported prevalence of up to 9.1%.[1] Acute lesions typically demonstrate erythema and pruritus, progressing to scaling and lichenification in chronic disease.[1] Patients often experience diminished quality of life; however, many achieve clearance with proper management and avoidance of known triggers.[1]

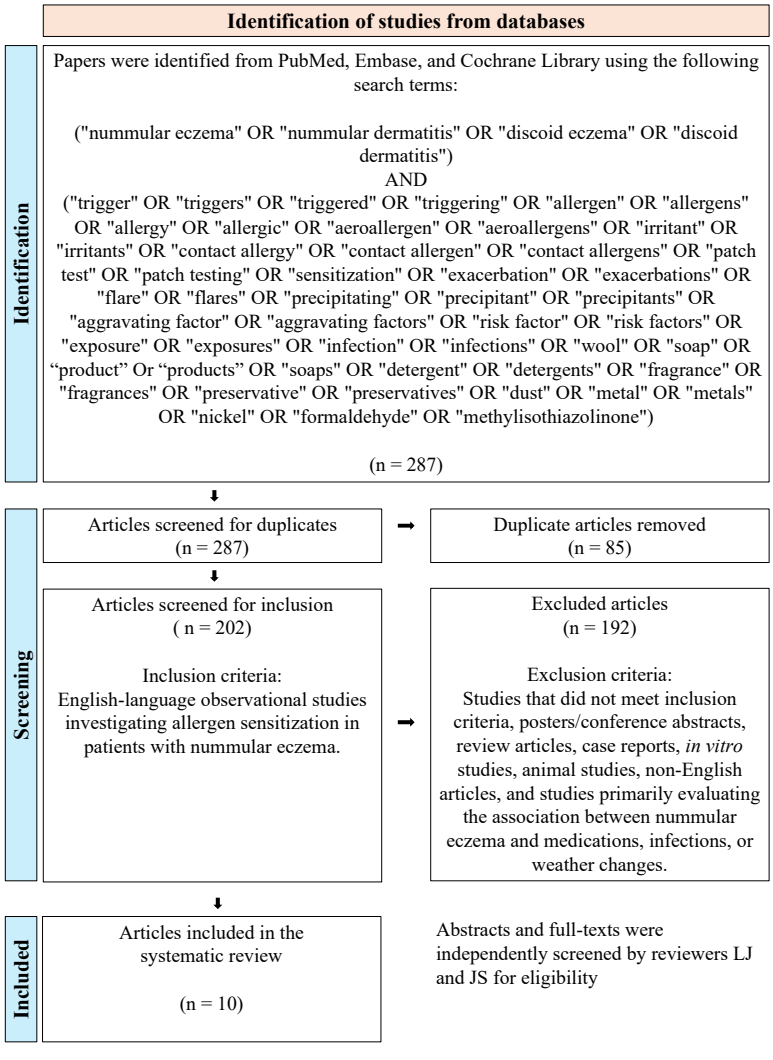
While the etiology of NE remains incompletely defined, NE exhibits clinical and immunologic overlap with atopic dermatitis (AD), sharing 4.3% of differentially expressed genes.[2] Immunologically, NE presents with features of Th2- and Th17-mediated inflammation, suggesting a complex inflammatory profile that converges with other eczematous and psoriasiform dermatoses.[2] NE is further characterized by a distinct, multifactorial pathophysiology involving epidermal barrier dysfunction and environmental exposures.[1,3] Impairment of the skin barrier may facilitate increased penetration of external irritants and allergens, contributing to immune cell activation, secondary infection, and disease exacerbation.[1,4]

NE has also been linked to several potential triggers, including xerosis, *Staphylococcus aureus* colonization, stress, and alcohol use.[5] Recent evidence further suggests a notable association between NE and allergic contact dermatitis (ACD), with several studies demonstrating high rates of contact sensitization in patients diagnosed with NE.[5,6] Patch testing in this patient population can be useful for identifying clinically relevant allergens.[7] Despite increasing recognition of the role contact sensitization plays in NE, the most commonly involved allergens and their clinical relevance remain incompletely defined. Herein, we systematically reviewed the available clinical evidence on allergens associated with NE and characterized patterns of contact sensitization within this population.

MATERIALS AND METHODS

A systematic search of PubMed, Embase, and Cochrane Library was conducted on April 30, 2026, per Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] guidelines (Figure 1).

FIGURE 1. PRISMA flow diagram for the systematic review of contact allergens and aeroallergens associated with nummular eczema.



RESULTS

The search yielded 287 papers. Two reviewers (LJ and JS) independently screened titles, abstracts, and full texts, resulting in 10 included studies. This research evaluated the patch test sensitivity of NE patients to the most commonly encountered allergens. Study characteristics are summarized in Table 1.

Among studies reporting the overall patch test positivity, Khurana et al reported the highest rate in patients with NE (56%), most commonly to potassium dichromate, nickel, cobalt chloride, and fragrance mix.[7] Fleming et al noted a similar patch test positivity rate (50%), with the most common allergens being rubber chemicals, nickel, formaldehyde, neomycin, Dowicil, and chrome.[8] Krupa Shankar et al reported positive reactions in 46% of NE patients, most commonly to colophony, nitrofurazone, neomycin sulfate, and nickel sulfate.[9] In a larger Italian retrospective cohort, Bonamonte et al identified at least one positive allergen in 32.5% of patients, with the highest sensitization rates observed for nickel sulfate, potassium dichromate, cobalt chloride, and paraphenylenediamine.[6] Jiamton et al also identified current or past patch test positivity in 50% of patients, most commonly due to nickel, rubber, fragrance, and gold.[10] Vigneshkarthik et al evaluated patients specifically with discoid hand eczema and detected positive patch testing in 26.7% of patients, mostly to potassium dichromate.[11] Furthermore, Silverberg et al found that NE patients had a lower proportion of patch test positivity than others in the North American Contact Dermatitis Group (49.5% vs 65%; $P<0.0001$), but nearly 1/4 had concomitant ACD; the most clinically relevant positive allergens included formaldehyde, methylisothiazolinone, quaternium-15, fragrance mix 1, and propylene glycol.[5] Similarly, Sari et al also reported a patch test positivity of 49.5%, particularly to carba mix, colophony, neomycin sulfate, Balsam of Peru, cobalt chloride, fragrance mix 1, paraben mix, and nickel sulfate.[12]

TABLE 1.

Summary of Studies Meeting Inclusion Criteria

Author (Year)	Study type (LOE)	Participants	Country	Measure of Exposure	Patch Test Series	Key Findings	Occupational Relevance
Fleming (1997)[8]	Cross-sectional study (LOE: 4)	48 patients with severe or persistent NE (mean age: 45)	United Kingdom	Patch testing	Particular series not specified	24 (50%) patients with positive patch tests, of which 16 (33%) were clinically relevant Most common allergens were rubber chemicals, nickel, formaldehyde, neomycin, Dowicil, and chrome (5, 3, 2, 2, 2, 2, respectively) Significantly more participants indicated that patch testing was worthwhile (P<0.001) No difference between males and females in type of allergen positivity 33% patients also had ACD	Most common occupations were retired (7), housewife (6), joiner (3), nurse (2), school student (2), driver (2), and bookkeeper (2) Among patients with clinically relevant positive patch tests, the most common occupations were housewife (5) and school (2)
Aoyama (1999)[13]	Case-control study (LOE: 3b)	26 NE elderly patients (mean age: 71); 21 age-matched controls; 43 young controls	Japan	Prick tests and patch tests	Particular series not specified	Prick tests: NE patients demonstrated *D. farinae* and house dust reactivity rates (35% and 12%, respectively) comparable to age-matched controls Both NE patients and age-matched controls showed significantly higher *C. albicans* reactivity than younger controls (P<0.01) Patch tests: patients with NE demonstrated higher percentage of positive patch tests to *D. farinae*, house dust, and *C. albicans* than the age-matched controls (46%, 35%, and 85%, respectively, P<0.05) and demonstrated either comparable or higher patch test positivity than young controls	Not specified
Khurana (2002)[7]	Cross-sectional study (LOE: 4)	40 NE patients (mean age: 36 years)	India	Patch testing	Indian Standard Series, approved by the Contact and Occupational Dermatosis Forum of India and interpreted according to International Contact Dermatitis Research Group criteria	28/50 (56%) patients demonstrated patch positivity to 1 or more allergens The most common allergens included potassium dichromate (20%), nickel (16%), cobalt chloride, and fragrance mix (12% each) Men tended to more commonly develop a single sensitization (50%) than two or three (35.7% and 14.3%, respectively) while women showed greater sensitization to two allergens (50%) than to a single allergen (21.4%) 34% patients also had ACD	Patients included farmers (24%), housewives (18%), students (14%), housewives engaged in farming (12%), shopkeepers (10%), laborers (8%), and a miscellaneous group including technicians, drivers, cable operators, office workers, and computer operators (14%)
Krupa Shankar (2005)[9]	Cross-sectional study (LOE: 4)	50 NE patients (mean age: 38.04)	India	Patch testing	Indian Standard Series, interpreted according to International Contact Dermatitis Research Group criteria	23/50 (46%) patients demonstrated patch test reactions Most patients demonstrated positive patch tests for colophony, nitrofurazone, neomycin sulfate, and nickel sulfate (7.14% each) Reactions to topical exposures accounted for approximately 64% of positive reactions, including topical medications (35.7%), cosmetic antigens (17.9%), and toiletry antigens (10.7%)	Not specified
Bonamonte (2012)[6]	Cross-sectional study (LOE: 4)	1022 NE patients (age range: 5–20)	Italy	Patch testing	Società Italiana di Dermatologia Allergologica Professionale e Ambientale baseline series, scored according to the International Contact Dermatitis Research Group guidelines	332/1022 (32.5%) patients demonstrated positive reactions to 1 or more allergens Highest rates of sensitization were found for nickel sulfate (10.2%), potassium dichromate (7.3%), cobalt chloride (6.1%), and paraphenylenediamine (5.8%) Sensitization incidence was higher in women (54.8%) than in men (45.2%)	NE was most commonly found in unskilled laborers, housewives, and hairdressers
Jiamton (2013)[10]	Cross-sectional study (LOE: 4)	100 NE patients (mean age 42 years)	Thailand	Patch testing	Particular series not specified	50% of patients had history and/or positive patch test Most common allergen was nickel (63%), rubber (14%), fragrance (14%), and gold (12%) Half of patients had past and/or current positive patch test, of which 12% of these had clinical relevance The condition was exacerbated by emotional stress and alcohol NE was associated with moderate quality-of-life impairment (mean DLQI of 9.2 ± 6.8) 49% patients had a possible history of ACD	NE presented most commonly in office workers (47%), laborers (24%) and traders (13%)

TABLE 1. (CONTINUED)

Summary of Studies Meeting Inclusion Criteria							
Author (Year)	Study type (LOE)	Participants	Country	Measure of Exposure	Patch Test Series	Key Findings	Occupational Relevance
Vignesh-karthik (2016)[11]	Cross-sectional study (LOE: 4)	54 hand eczema patients; 15 discoid hand eczema patients (age not reported)	India	Patch testing	Indian Standard Series, approved by Contact and Occupational Dermatoses Forum of India	Patch test was positive in 4 participants (26.7%) 3/4 NE patients had a positive patch test to potassium dichromate NE patients were significantly more likely to have a positive patch test reaction to potassium dichromate (P=0.02) 11/31 patients with past exposure to detergents demonstrated positive patch testing	Among all patients, the most common occupational groups were housewives (26%), agriculturists (17%), students (11%), masons (9%), and housekeeping staff (4%) Potassium dichromate allergy was significantly associated with masons (2/5; P=.02), and para-phenylenedi-amine allergy was significantly associated with hair dye use (2/3; P=0.012)
Indrastuti (2019)[14]	Case-control study (LOE: 3)	42 NE patients (mean age: 27.48); 42 healthy controls	Indonesia	Nickel skin patch testing	International Contact Dermatitis Research Group criteria	Nickel contact allergy was significantly different between NE group and healthy controls demonstrated by multivariate analysis with conditional logistic regression (OR 9.63; 95% CI 1.02-109.38; P=0.04) A participant with a positive nickel patch test has a 9.63 times higher risk of having NE	Not specified
Silverberg (2021)[5]	Cross -sectional study (LOE: 4)	38,723 patients from the North American Con-tact Dermatitis Group (NACDG) (mean age: 48); 748 NE patients	North America	Patch testing and significance-prevalence index num-ber (SPIN; measure of allergen rel-evance and prevalence)	Standardized NACDG screening allergens + some non-NACDG allergens	Patients with NE had lower proportion of ≥1 positive allergen sensitivity than those without NE (49.5% vs 65%; P<0.0001) The allergens which were most clinically relevant in patients with any NE diagnosis were formaldehyde 2.0% aqueous, methylisothiazolinone, quaternium 15, fragrance mix 1, and propylene glycol Among patients with NE, 68.9% had isolated NE Patients also had concomitant ACD (23.9%), irritant contact dermatitis (3.5%), and AD (3.7%) NE occurrence was associated with increased age and male sex Children comprised <1% of patients with NE referred for patch testing	462 NE patients with occupation data were employed Employment was significantly associated with NE diagnosis (OR 1.279, P=0.0098)
Sari (2023)[12]	Cross-sectional study (LOE: 4)	616 participants (mean age: 36.5 years), 48 NE patients	Indonesia	Patch testing	Particular series not specified	49.5% of patients with any NE diagnosis had a positive patch test Most NE patients demonstrated positivity to carba mix (29.17%), colophony (24.14%), neomycin sulfate (21.88%), Balsam of Peru (17.39%), cobalt chloride (16.67%), fragrance mix 1 (15.63%), paraben mix (13.33%), and nickel sulfate (13.27%)	Not specified

DISCUSSION

While the etiology of NE remains elusive, emerging literature suggests that exogenous factors may contribute to disease onset, persistence, or exacerbation.[10] Xerosis, impaired barrier function, infection, stress, alcohol use, occupational exposure, and contact sensitization have all been proposed as relevant contributors.[9,10,13] Nevertheless, few studies have evaluated the relationship between NE and contact sensitization or characterized the allergens most frequently implicated in this population. This systematic review found that contact allergen sensitization is common among patients with NE. Although reported rates vary across studies, these differences likely reflect differences in geography, patient population, and patch test series used.

Patch Test Positivity and Allergen Types

Across studies with available data, overall patch test positivity among patients with NE ranged from 26.7% to 56.0%, with a median of 47.8%. The most frequently implicated patch test allergens overall were nickel and nickel sulfate, potassium dichromate, cobalt chloride, fragrance mix, neomycin, colophony, formaldehyde, paraphenylenediamine, and rubber-related allergens. Furthermore, the studies demonstrated that ACD is relatively common in patients with NE. Among the 4 studies explicitly reporting ACD diagnosis, a median of 33.5% (range: 23.9% to 34.0%) of patients with NE also had concurrent ACD or a history of ACD. Nevertheless, further research is needed to elucidate whether NE itself is associated with allergen sensitivity or whether NE patients develop concomitant ACD.

Nickel and nickel sulfate were among the most consistently reported allergens in the included studies (n=7). Nickel sensitization was independently associated with NE in a case-control study by Indrastuti et al (OR 9.63; 95% CI 1.02-109.38; P=0.04), corresponding to 9.63-fold higher odds of NE among nickel-sensitized participants.[14] Other observational studies have also reported nickel patch test positivity in as high as 63% of NE patients.[10] Other metal-related allergens, including cobalt and potassium dichromate, also emerged as recurrent allergens across studies. Within this context, laundry detergent is a common source of allergen sensitivity.[11] Patients with a history of detergent use demonstrated positive patch testing to

nickel, paraphenylenediamine, and cobalt, among others.[11] We have found that routine household products, such as laundry detergents, may be clinically relevant but underrecognized contributors in patients with NE.

Fragrance-related allergens, including fragrance mix and Balsam of Peru, were commonly reported. Fragrance mix 1 comprises 8 fragrance compounds commonly found in personal care products, detergents, perfumes, lotions, and occupational exposures.[11] Rubber chemicals were also frequently implicated and may reflect exposure to gloves, footwear, or other elastic materials in routine use.[8,10] Relevant topical preservatives in patch testing included formaldehyde and quaternium-15. Formaldehyde exposure may arise from personal care products, cleaning products, fabrics, paints, and medications.[5] Formaldehyde has also been implicated as a potential cause of systemic contact dermatitis.[5] While the mechanistic role of these allergens in NE remains undefined, researchers have hypothesized that they promote cutaneous Th17 and/or Th2 immune responses, which are upregulated in NE.[5]

Occupational and lifestyle patterns further support the importance of obtaining a thorough exposure history with NE patients. One study demonstrated that employment was significantly associated with NE diagnosis (OR 1.279, P=0.0098), with housework being the most consistently reported occupational exposure.[5] Studies found that housewives were among the most prevalent patients with clinically relevant positive patch test results, likely due to exposure to cleaning products and associated equipment.[8] Other notable professions included farmers, agriculturists, masons, and laborers.[6,7]

Patch testing should be considered in all patients with severe or treatment-refractory NE. Allergen avoidance could lead to substantial improvement or resolution in selected patients. Accordingly, a thorough household and occupational exposure history should be obtained during the medical interview. Clinicians are encouraged to routinely ask patients regarding their use of certain fragranced hygiene products, cosmetics, detergents, jewelry, and occupational exposures. Fleming et al reported that a significant proportion of patients with positive patch test results perceived patch testing as beneficial (P<0.001).[8] Patch testing may improve the quality of life in patients with chronic recalcitrant NE.[9] Regardless of whether contact sensitization directly causes NE or represents concomitant ACD, patch testing may identify clinically relevant exposures and guide allergen avoidance.

Limitations

This systematic review is limited by the predominance of cross-sectional studies and heterogeneity in study design, patient populations, and patch test series. Studies were also conducted across diverse participant populations. Since allergen exposure patterns vary by geographic region, occupation, cultural practices, product use, and environmental factors, findings may not be comparable between studies. NE is also a clinical diagnosis without a standardized diagnostic protocol, which can lead to misclassification of NE with morphologically similar conditions.

CONCLUSION

Available observational evidence suggests that contact allergen sensitivity is common among patients with NE. These findings support the use of patch testing in appropriately selected NE patients to identify clinically relevant allergens, guide trigger avoidance strategies, and potentially reduce disease persistence or recurrence. Further studies using standardized patch testing and comprehensive allergen assessment are needed to clarify whether contact sensitization is a primary etiologic factor, a secondary aggravator, or a comorbid finding in NE.

DISCLOSURES

None of the authors has conflicts of interest to disclose.

ACKNOWLEDGMENT

LJ performed the literature search and wrote the main manuscript. LJ and JS reviewed the studies independently. JS and JJ helped to edit the final manuscript. All authors reviewed and approved the final manuscript.

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Current
Clinical Solutions

October 2026

Bemotrizinol: A Next-Generation Broad-Spectrum Ultraviolet Filter Enters the United States Sunscreen Armamentarium

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Supported by La Roche-Posay.

Distributed by
JOURNAL OF DRUGS IN DERMATOLOGY
JDD

Abstract

Background: The US sunscreen landscape has long lagged behind global counterparts, with no new organic ultraviolet (UV) filter approved since ensulizole in 1999. This regulatory stagnation has left American formulators with an inadequate toolkit for UVA protection, photostability, and cosmetic elegance.

Objective: To review the photochemistry, clinical safety, and dermatologic utility of bemotrizinol (bis-ethylhexyloxyphenol methoxyphenyl triazine; BEMT), the first new organic UV filter added to the US over-the-counter (OTC) sunscreen monograph in more than 2 decades.

Methods: Synthesis of published photobiological, pharmacokinetic, and clinical data submitted to and reviewed by the FDA, as well as peer-reviewed literature.

Results: BEMT is a photostable, oil-soluble, broad-spectrum UV filter with dual absorption peaks at approximately 310 nm (UVB) and 343 nm (UVA1), bridging the historically underprotected 320-nm transition gap. Its high molecular weight (627.8 g/mol) confers negligible systemic absorption. Across 472 participants in 4 clinical trials, BEMT demonstrated no contact sensitization, phototoxicity, photoallergenicity, or systemic accumulation. It photostabilizes avobenzone via triplet-triplet energy transfer, is compatible with all existing UV filters including zinc oxide and titanium dioxide, and provides transparent application with no white cast.

Conclusions: BEMT represents the most meaningful advance in US photoprotection in over 25 years, with particular relevance for patients with pigmentary disorders and individuals with skin of color. Its approval, effective August 9, 2026, warrants prompt integration into dermatologic practice.

Introduction

For more than 2 decades, US dermatologists have counseled patients on sun protection within the constraints of a sunscreen monograph that had effectively stood still. While the European Union, Australia, and many Asian markets have access to more than 29 approved UV filters, the US has permitted only 16 active sunscreen ingredients, with the last new organic (chemical) filter, ensulizole, approved in 1999.[1,2]

The consequences of this regulatory gap have been clinically meaningful. Avobenzone, approved in 1988, remains the sole FDA-monographed filter with meaningful long-wavelength UVA1 (340–400 nm) coverage. Yet avobenzone is inherently photounstable and cannot be combined with mineral filters such as zinc oxide (ZnO) and titanium dioxide (TiO_2) in sunscreen formulations marketed in the US. Moreover, the existing US filter portfolio leaves an inadequately protected spectral zone near 310–340 nm, a transitional region between UVB and UVA2 wavelengths where photodamage, including DNA strand breaks and the stimulation of melanogenesis, is clinically relevant.[2]

The regulatory pathway itself was a barrier. Under the legacy OTC monograph system, new sunscreen active ingredients required exhaustive, multi-year data submissions with no defined timeline for agency action, a process that had effectively frozen US innovation since the 1990s. The Coronavirus Aid, Relief, and Economic Security (CARES) Act of 2020 changed the regulatory landscape, replacing it with an administrative order pathway that established clear timelines and review standards.[1]

On June 9, 2026, the FDA issued final administrative order OTC000039, formally adding bemotrizinol (BEMT) to OTC sunscreen monograph M020, a milestone 25 years in the making. This order took effect August 9, 2026, initiating an 18-month marketing exclusivity period for DSM-Firmenich's proprietary brand, PARSOL Shield.[1]

This review provides dermatologists with a comprehensive understanding of BEMT's photochemistry, clinical safety profile, formulation advantages, and practical implications for patient care.

The BEMT Molecule: Chemistry, Absorption Profile, and Photostabilization Mechanisms

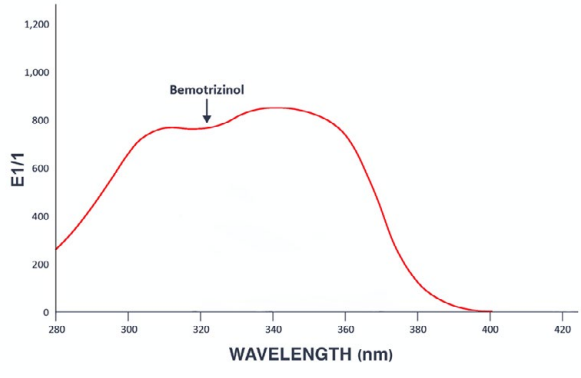
Chemical Identity and Physical Properties

Bemotrizinol is chemically designated as bis-ethylhexyloxyphenol methoxyphenyl triazine (CAS 187393-00-6). Its structural core is a central 1,3,5-triazine ring symmetrically substituted with 3 aromatic moieties: one 4-methoxyphenyl group and two 2-hydroxyphenol groups, each etherified with 2-ethylhexyloxy chains at the 5-position.[3] BEMT has a molecular weight of 627.8 g/mol and presents physically as a pale yellow crystalline powder. It is highly lipophilic, insoluble in water but readily soluble in common cosmetic emollients, and is incorporated into the lipid phase of both oil-in-water and water-in-oil emulsions. Approved dosage forms include lotions, creams, oils, gels, butters, pastes, ointments, and sticks; non-aerosol sprays are permitted, while propellant-combined aerosol sprays and dry powders are not.[1]

UV Absorption Profile and the 320-nm Gap

BEMT exhibits a broad, continuous UV absorption spectrum spanning approximately 280 to 400 nm, with 2 distinct absorption maxima: approximately 310 nm in the UVB range and 343 nm in the UVA1 range (Figure 1).[2,3]

Figure 1. Ultraviolet absorption spectrum of bemotrizinol. Bemotrizinol (BEMT) demonstrates strong, continuous absorption across UVB and UVA, including UVA2 (320–340 nm) and UVA1 (340–400 nm).



This dual-peak profile is clinically significant. No currently available FDA-approved UV filter provides reliable, photostable coverage across both of these peaks simultaneously, a deficiency most conspicuous in the 310–340 nm transitional region between UVB and UVA2. This spectral zone has been termed the "320-nm gap" in the US filter portfolio.[2] Radiation in this range is biologically active: it contributes to cyclobutane pyrimidine dimer formation, oxidative DNA damage, and the initiation of melanogenic signaling pathways. BEMT's continuous absorption across this transition directly addresses a longstanding gap in US photoprotective coverage.

Intrinsic Photostability: The ESIPT Mechanism

Unlike some organic UV filters that degrade upon UV exposure, BEMT is intrinsically photostable by virtue of a rapid excited-state intramolecular proton transfer (ESIPT) mechanism.[3]

Upon absorbing a UV photon, the BEMT molecule transitions from its ground singlet state to an excited singlet state. Rather than degrading or generating reactive oxygen species (ROS), it dissipates this absorbed energy through a non-radiative intramolecular proton transfer: the phenolic hydroxyl proton is transferred to an adjacent nitrogen atom on the triazine ring, converting the enol tautomer to an excited keto tautomer. This keto form undergoes rapid internal conversion, releasing the absorbed energy as harmless heat and vibrational energy before the molecule returns to the stable enol ground state. The entire photocycle occurs on a picosecond timescale and does not involve covalent bond homolysis, ensuring that BEMT neither degrades nor sensitizes adjacent molecules over the product's lifetime.

Photostabilization of Avobenzone

Beyond its own photostability, BEMT serves as a potent photostabilizer for avobenzone—the most widely used UVA filter in the US market. Avobenzone is a dibenzoylmethane derivative that absorbs maximally at approximately 360 nm but is highly photolabile: upon UV exposure, it undergoes irreversible photodegradation, losing approximately 60% of its UVA-filtering capacity within 1 hour of sunlight exposure.[4]

BEMT prevents this degradation through a triplet-triplet energy transfer mechanism. When avobenzone enters its reactive triplet excited state, the precursor to homolytic cleavage, BEMT accepts the excitation energy through a collisional, non-radiative transfer and dissipates it via its own ESIPT pathway. Formulations pairing BEMT with avobenzone retain more than 90% of avobenzone's UVA protection after prolonged sun exposure.[4] Critically, BEMT also demonstrates compatibility with ZnO and TiO_2, which normally accelerate avobenzone photodegradation, an incompatibility that has severely constrained US mineral sunscreen formulation for decades.[2]

Safety Profile

Systemic Absorption and the 500 Dalton Rule

A defining safety advantage of BEMT is its negligible systemic absorption. The "500 Dalton rule" of dermal pharmacology holds that molecules exceeding 500 g/mol encounter significant resistance to penetrating the intact stratum corneum. BEMT's molecular weight of 627.8 g/mol places it well above this threshold, and this structural prediction is borne out clinically.[2]

In contrast, legacy UV filters such as oxybenzone (228.2 g/mol) are small enough to cross the dermal barrier. These filters have demonstrated systemic plasma concentrations exceeding the FDA's threshold of concern (0.5 ng/mL) under maximal use conditions in randomized clinical trials[5], raising legitimate questions about chronic exposure. BEMT does not share this liability.

Clinical Trial Program

To support its GRASE determination, BEMT was evaluated in a 4-trial clinical development program enrolling 472 participants.[1]

The pharmacokinetic program began with BEMT-001 Part 1 (Pilot Maximal Use Trial, MUsT), an open-label, single-arm study in 14 healthy adults (7 male, 7 female). Participants applied a model sunscreen containing 6% BEMT with 10% ethanol, a vehicle specifically designed to maximize potential skin penetration, multiple times daily for 4 days. Of the 299 plasma samples analyzed, 92.6% were below the limit of quantification (<0.1 ng/mL), and BEMT was entirely undetectable in 50% of participants, with no evidence of accumulation.[3]

The BEMT-001 Part 2 (Pivotal MUsT) trial randomized 162 healthy adults across 3 parallel arms to evaluate cream, lotion, and oil vehicles containing 6% BEMT, each applied to 75% or more of body surface area 4 times daily for 4 days, conditions explicitly designed to simulate worst-case real-world use. Plasma concentrations consistently remained below the FDA's 0.5 ng/mL threshold of concern across all 3 vehicles and throughout the treatment period, confirming negligible systemic bioavailability under maximal conditions.[1,3]

Local Tolerability

Local tolerability of 6% BEMT was evaluated across a comprehensive battery of dermatologic safety studies. A human repeated insult patch test (HRIPT) and cumulative irritation study found no primary sensitization. Dedicated phototoxicity and photoallergenicity trials, both conducted under standardized solar-simulated UV light exposure, produced no phototoxic or photoallergic cutaneous reactions.[1]

An independent study conducted at laboratories extended these findings in 54 adult participants (8 male, 46 female; age 18–65) subjected to occlusive patch application for 24 hours, 3 times weekly for 3 consecutive weeks, followed by a 10 to 14-day rest period and re-challenge. The study confirmed the absence of any irritant or sensitizing potential even under occlusive conditions, a rigorous standard that exceeds typical consumer use.[1]

Long-term and Reproductive Safety

A 104-week dermal carcinogenicity study in rodents, using daily doses up to the highest feasible concentration, revealed no treatment-related systemic toxicity, target organ effects, or neoplastic changes. Multigenerational reproductive toxicity assays demonstrated no adverse effects on reproductive performance or offspring development. The FDA granted GRASE status for use in adults and children 6 months of age and older.[1]

Key Advantages and Clinical Benefits

Formulation Versatility

BEMT's oil solubility and compatibility with the full spectrum of existing UV filters, including ZnO, TiO_2, avobenzone, octocrylene, homosalate, octisalate, and ensulizole, give formulators an unprecedented degree of flexibility. The ability to pair BEMT with mineral filters, historically precluded by avobenzone's incompatibility with ZnO and TiO_2, enables a new generation of hybrid sunscreens that can achieve high SPF values and superior UVA protection at lower overall active concentrations. Reducing mineral filter concentrations also directly improves cosmetic elegance by reducing visible whitening—a benefit with real-world adherence implications.[2]

BEMT's solubility in polar lipids and common cosmetic emollients (such as octisalate, homosalate) prevents recrystallization in formulation over the product's shelf life, contributing to consistent UV performance from first to last use.

Pigmentary Disorders: Melasma and Post-Inflammatory Hyperpigmentation

Melasma and post-inflammatory hyperpigmentation (PIH) represent among the most treatment-resistant conditions in clinical dermatology, with disproportionate impact on patients with Fitzpatrick phototypes III–VI. A key driver of therapeutic failure is the inability of currently available US sunscreens to provide comprehensive, durable protection across the full spectrum of melanogenic radiation.

UV-driven melanogenesis is not confined to UVB. Long-wavelength UVA1 radiation (340–400 nm) and high-energy visible light (HEVL, 400–440 nm) activate melanocytes through distinct signaling cascades. HEVL is detected by the opsin-3 (OPN3) receptor on melanocytes, triggering a transient receptor potential vanilloid 1 (TRPV1)-mediated calcium influx, downstream CaMKII activation, ERK pathway upregulation, and ultimately MITF-driven transcription of tyrosinase, resulting in pigment synthesis that can persist for up to 22 days after a single exposure. Mineral sunscreens can reduce HEVL but are limited by the cosmetic barrier of white cast in darker skin tones.

BEMT directly addresses the UVA1 component of this pathway. Its photostable absorption peak at 343 nm provides continuous, reliable coverage of the UVA1 spectrum without degrading over a day of outdoor exposure. Unlike formulations relying solely on avobenzone for UVA1 coverage, where photodegradation progressively erodes protection as the day advances, BEMT-containing formulations maintain their UVA1 filtering capacity throughout prolonged sun exposure.[4]

Perhaps equally important is BEMT's cosmetic profile. Patients with darker skin phototypes have historically cited the white cast of mineral-dominant sunscreens as a primary barrier to consistent daily use, and incomplete sunscreen use is a well-documented driver of melasma recurrence and treatment failure. BEMT is a chemical filter that applies completely transparently. Its incorporation into formulations enables high-SPF, broad-spectrum sunscreens that are cosmetically acceptable across all skin tones, reducing a structural barrier to compliance and, by extension, improving clinical outcomes for melasma and PIH.[1,2]

Environmental Considerations

The environmental safety of sunscreen actives has attracted increasing social media attention, particularly following anecdotal reports that oxybenzone and octinoxate can induce coral bleaching, disrupt marine endocrine systems, and bioaccumulate in aquatic food chains. Hawaii and several other jurisdictions have banned the 2 above filters outright.

BEMT's physicochemical profile confers a meaningfully different environmental risk profile. Its high molecular weight and extreme water insolubility limit its ability to dissolve in and distribute through the water column, reducing the potential for marine bioaccumulation. Toxicological studies have shown that BEMT does not induce coral bleaching or DNA damage in marine organisms at environmentally relevant concentrations.[1]

Based on a weight-of-evidence evaluation integrating environmental exposure, bioavailability, and ecotoxicological effects, the proposed use of bemotrizinol at concentrations up to 6% in over-the-counter sunscreen products is not expected to result in significant adverse effects on the quality of the human environment. All risk characterizations, including worst-case exposure scenarios, demonstrate adequate margins of safety.

Modernizing the US Formulation Toolkit

US sunscreen formulators have long operated with fewer UV filters that are available in other parts of the globe. While European manufacturers can draw on 29 approved UV filters to engineer formulations of varying elegance, SPF, and UVA protection, the US counterparts have been limited to approximately 7 commonly used active ingredients. This disparity has not merely been a commercial inconvenience; it has imposed real constraints on the quality of photoprotection available to American patients.[1,2]

The approval of this new UV filter was by DSM-Firmenich, a project that was carried out over 8 years and cost millions of dollars. The initial market availability will be under DSM-Firmenich's PARSOL Shield branding, protected by an 18-month exclusivity period running through approximately February 2028. After exclusivity expires, broader uptake by competing manufacturers is expected, and BEMT-containing products will become widely available across price points.[1]

From a business standpoint, DSM-Firmenich's decision to pursue this pathway is somewhat unconventional. Unlike a novel drug approval, which typically confers decades of patent-protected market exclusivity, the FDA's OTC monograph process affords no such durable protection; BEMT is not a novel, patentable molecule, and the resulting 18-month exclusivity window is brief relative to the multi-year investment and cost required to bring it through review. This process raises a broader question of precedent: will other UV filter manufacturers be willing to undertake a similarly resource-intensive regulatory odyssey, knowing that any competitive advantage gained will be short-lived? If not, it is conceivable that few, if any, additional internationally available UV filters will reach the US market unless another manufacturer is willing to make a comparable investment without the assurance of long-term exclusivity.

Viewed in this light, DSM-Firmenich's decision to proceed despite this asymmetry between investment and protection deserves recognition: the company appears to have advanced this filter through the regulatory process on the premise that expanding UV protection options serves public health in the US, rather than for the promise of durable commercial return.

Conclusion

Bemotrizinol's approval marks the end of a 25-year hiatus in US sunscreen innovation. For dermatologists and their patients, it arrives not as an incremental refinement but as a substantive expansion of the photoprotective toolkit, one that simultaneously addresses the spectral coverage gap at 310–340 nm, the chronic photostability limitations of avobenzone, the formulation incompatibilities between chemical and mineral UV filters, and the cosmetic elegance barrier that has undermined sunscreen adherence in patients with skin of color.

Its safety profile is robust. With a molecular weight far exceeding the 500 Dalton dermal penetration threshold, negligible systemic absorption across 4 clinical trials, and no evidence of sensitization, phototoxicity, or carcinogenicity, BEMT satisfies the stringent standards the FDA appropriately applies to topical drugs applied repeatedly to broad body surface areas.

Clinically, dermatologists should begin counseling appropriate patients—particularly those with high risks for skin cancers, melasma, PIH, or other conditions requiring reliable broad-spectrum UVA1 photoprotection, on the availability of BEMT-containing sunscreens as of August 9, 2026. Early products will carry the PARSOL Shield ingredient designation. As market exclusivity expires in early 2028, BEMT incorporation across the sunscreen market will expand significantly.

The BEMT approval represents a lengthy and costly undertaking, carried out under the CARES Act modernization pathway. While this pathway was designed to deliver rigorous, science-based decisions on novel UV filter candidates within a timeframe that does not discourage investment, the BEMT experience suggests that further refinement may be warranted. An 8-year, multi-million-dollar effort, yielding only a comparatively brief period of market exclusivity, may not provide sufficient incentive for other manufacturers to bring additional, well-characterized UV filters already in global use through the same process. The dermatologic community should advocate for continued evolution of this pathway, with the goal of building a US sunscreen landscape that more efficiently reflects the state of international photobiological science.

Disclosure

Dr Wang has served as a consultant for ISDIN, Kenvue, La Roche-Posay, and Coppertone. Mr Osterwalder and Ms Waske have no conflicts of interest to disclose.

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doi:10.36849/JDD.9756

October 2026 919 Volume 25 • Issue 10

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Biologics and Small-Molecule Inhibitors for the Treatment of Nummular Eczema: A Systematic Review

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ABSTRACT

Background: Nummular eczema (NE) is a chronic, pruritic dermatitis with substantial patient burden and no FDA-approved therapies. Emerging data suggest that biologics and small-molecule inhibitors may be promising therapeutic options for NE.

Methods: On October 29, 2025, PubMed, Embase, and the Cochrane Library were searched using PRISMA guidelines for English-language human clinical studies and cases evaluating biologics and small-molecule inhibitors for the treatment of NE.

Results: Of 219 studies identified, 10 met the inclusion criteria. Grade of recommendation: B supporting dupilumab and tralokinumab. Grade of recommendation: C supporting roflumilast and delgocitinib. Grade of recommendation: B against apremilast.

Conclusions: Current evidence supports dupilumab and tralokinumab for the treatment of NE. Roflumilast and delgocitinib should be reserved for selected cases, and apremilast is not recommended. Randomized controlled trials are needed to establish optimal treatment for patients with NE.

J Drugs Dermatol. 2026;25(10):919-924. doi:10.36849/JDD.9756

INTRODUCTION

Nummular eczema (NE) or discoid eczema is an idiopathic chronic dermatitis characterized by pruritic, coin-shaped lesions often affecting the extremities.[1] NE frequently follows a relapsing course, is intensely pruritic, and can substantially impair quality of life.[2] NE is the third most common noncommunicable inflammatory skin disease, after atopic dermatitis (AD) and psoriasis, with an estimated prevalence of 0.1-9.1%.[1,2] Potential triggers of NE have been identified as cutaneous microbial colonization, long-standing contact dermatitis, systemic retinoid therapy, and excessive alcohol use.[1]

Although previously classified as a variant of AD, NE is characterized by unique clinical and histological markers.[3] Unlike AD, which is predominantly mediated by a Th2 immune response, NE displays a Th2/Th17 immunologic profile and closely aligns with psoriasis, as evidenced by its well-demarcated erythematous plaques and scaling.[3,4] Histologically, NE exhibits increased eosinophils and spongiosis similar to AD, as well as epidermal hyperplasia, parakeratosis, and neutrophilic infiltration similar to psoriasis.[1,5] One study demonstrated that NE shares 16% of differentially expressed genes with psoriasis, while only 4.3% with AD.[1] NE's immunologic, histologic, and genetic profiles suggest that the dermatitis may respond to existing targeted psoriasis and atopic dermatitis therapies, which have shown efficacy in real-world practice.[6]

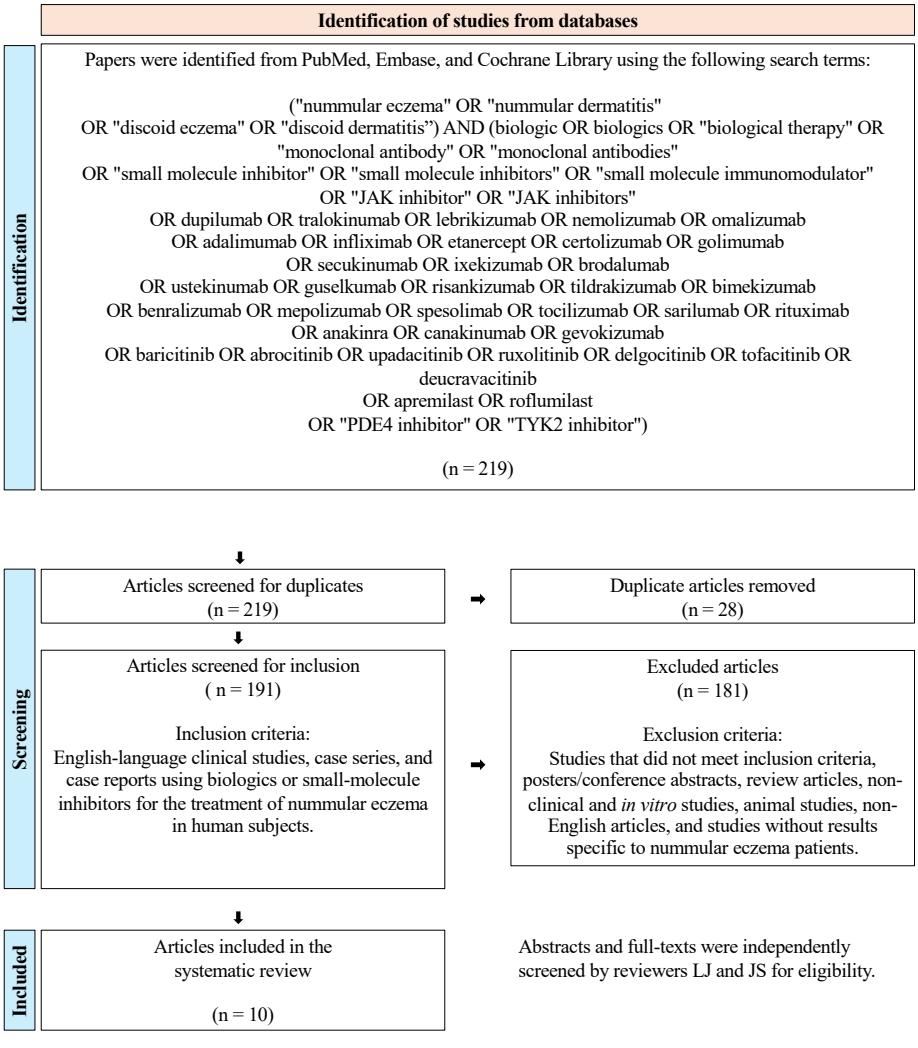
The current first-line treatment for NE is topical corticosteroids.[7] Corticosteroids are associated with side effects, including skin atrophy and telangiectasia.[8] Achieving remission remains challenging; patients frequently relapse and suffer from severe pruritus.[7] Therefore, new therapeutic strategies are warranted.

Despite NE's high prevalence and patient burden, the condition has been poorly researched, making its etiology and pathophysiology largely unknown. There is no FDA-approved treatment for NE, leaving a clear unmet need that demands urgent attention. Emerging research has demonstrated that biologics and small-molecule inhibitors, including Janus kinase (JAK) inhibitors and phosphodiesterase 4 (PDE4) inhibitors, represent promising therapeutics in the treatment of NE.[6,9] Herein, we summarize the safety and efficacy of biologics and small-molecule inhibitors evaluated in studies for the treatment of NE, describe their mechanisms of action, and identify gaps to inform future trial design and clinical implementation.

MATERIALS AND METHODS

A systematic search of PubMed, Embase, and Cochrane Library was conducted on October 29, 2025, according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] guidelines (Figure 1).

FIGURE 1. PRISMA flow diagram for the systematic review of biologics and small-molecule inhibitors for the treatment of nummular eczema.



RESULTS

Our search resulted in 219 papers. After screening the titles, abstracts, and full texts, 10 clinical studies and cases met the inclusion criteria. The research evaluated biologics and small-molecule inhibitors: dupilumab (7), tralokinumab (1), apremilast (1), roflumilast (1), and delgocitinib (1). Table 1 summarizes study characteristics. The medications are organized by grade of recommendation for NE.

DISCUSSION

Grade of Recommendation: B Supporting Treatment of Nummular Eczema

Dupilumab

Dupilumab is a biologic that has demonstrated safety and efficacy in the treatment of moderate-to-severe AD in patients 6 months and older.[10] Dupilumab is a human monoclonal antibody directed against the interleukin-4 receptor α subunit.[11]

We identified 5 retrospective cohort studies and 2 cases evaluating dupilumab for the treatment of NE. In a retrospective, single-center cohort study, 59 patients with NE were enrolled who were treated with dupilumab or tralokinumab for 52 weeks. As early as week 4, participants treated with dupilumab demonstrated significantly improved scores in Eczema Area and Severity Index (EASI-75), Pruritus Numerical Rating Scale (P-NRS), Sleep Disturbance NRS (SD-NRS), Dermatology Life Quality Index (DLQI), Atopic Dermatitis Control Tool (ADCT), and Patient-Oriented Eczema Measure (POEM), with consistent improvement until week 52 (P<0.001). The total proportion of patients achieving EASI-75 increased from 38.2% at week 4 to 86.5% at week 52. Patients experienced adverse events (AE), including eosinophilia, ocular manifestations, psoriasis, injection-site reactions, and arthralgias. Dupilumab was discontinued in 2 patients due to the development of new-onset psoriasis.[6]

TABLE 1.

Summary of Studies Meeting Inclusion Criteria for the Use of Biologics and Small-Molecule Inhibitors for the Treatment of Nummular Eczema

Author	Study Type/ Subjects	Intervention	Duration	Findings	Adverse Effects
Dupilumab					
Barei[6]	Retrospective cohort study (59 adult participants)	Dupilumab Tralokinumab (dosing not specified)	52 weeks	Significantly improved scores in EASI-75, P-NRS, SD-NRS, DLQI, ADCT, and POEM by week 4 for both dupilumab and tralokinumab treatment groups Consistent improvement until week 52	Transient eosinophilia (n = 4), ocular AEs (n = 5), psoriasis (n = 4), arthralgias (n = 1) and injection-site reaction (n = 1) Dupilumab was discontinued in 2 patients due to psoriasis
Choi[11]	Retrospective cohort study (6 adult participants)	Dupilumab (600 mg loading; 300 mg every two weeks)	2 years	5/6 patients experienced a decrease in body surface area involvement (≥90% improvement) throughout 2 years of follow-up	Discontinuation due to fluctuating response and the development of conjunctivitis (n=1)
Kim, E.[10]	Retrospective cohort study (14 children)	Dupilumab (dosing not specified)	variable	Significant clinical improvement in 12/14 children (median time: 2.5 months) POEM scores improved from a median of 23 at baseline to 2.5 at follow-up	Discontinuation due to new-onset psoriasis (n=1)
Patruno[12]	Retrospective cohort study (30 adult participants)	Dupilumab (dosing not specified)	16 weeks	Significantly improved EASI, DLQI, and visual analogue score of pruritus from baseline to week 16 (4.83, 4.03, and 1.23, respectively; $P<0.001$)	Conjunctivitis (n=1)
Tavecchio[13]	Retrospective cohort study (221 adult participants total; 8 with NE)	Dupilumab (600 mg loading; 300 mg every 2 weeks)	variable	Significantly improved EASI, DLQI, itch-NRS, and sleep-NRS scores after 16 weeks, persisting to week 52 (reduction percentages: 78.04%, 77.09%, 37.28%, 79.57%, respectively; $P<0.0001$)	Discontinuation due to inadequate response (n=2), severe conjunctivitis (n=1), elevated eosinophils (n=1), severe psoriasis (n=1), and a combination of elevated eosinophils, blepharitis, and conjunctivitis (n=1)
Kim, J.[14]	Case series (4 children total; 1 child with NE)	Dupilumab (600 mg loading; 300 mg every 2 weeks)	24 weeks	EASI and IGA improved from 24.7 and 4 at baseline to 0 by week 24	No AEs in NE patient Patient with prurigo nodularis developed conjunctivitis
Romiti[15]	Case report (1 child)	Dupilumab (300 mg monthly)	1 year	Substantial clinical improvement within 2 weeks, with complete clearance persisting after 1 year P-NRS decreased from 9 to 1	None
Tralokinumab					
Barei[6]	Retrospective cohort study (59 adult participants)	Tralokinumab Dupilumab (dosing not specified)	52 weeks	As early as week 4, participants treated with tralokinumab had significantly improved scores in EASI-75, P-NRS, SD-NRS, DLQI, ADCT, and POEM, with consistent improvement until week 52 ($P<0.001$)	Tralokinumab was discontinued in 5 patients due to inefficacy (n=2), injection-site reaction (n=1), and psoriasis (n=2)
Roflumilast					
Gyldenløve[9]	Case report (1 adult)	Oral roflumilast (500 µg daily)	24 weeks	Marked clinical improvement within 2 weeks Complete clearance at 4 weeks and maintained remission at 24 weeks	6 kg weight loss, nausea, loose stools, and headaches
Delgocitinib					
Kurokawa[21]	Case report (1 child)	Topical delgocitinib (undisclosed dose twice daily) and NB-UVB (400 mJ/cm2 once weekly)	8 weeks	Substantial clinical improvement, from an elevated, erythematous, brown lesion to a flat light-brown lesion	None
Apremilast					
Böhner[5]	Randomized, double-blind, placebo-controlled phase IIb study (31 participants)	Apremilast (30 mg twice daily) Matched placebo	32 weeks	One patient treated with apremilast and 4 patients given the placebo demonstrated improvement in PGA No differences overall between apremilast and placebo regarding PGA, EASI50, biopsy skin inflammation, quality of life, pruritus, transepidermal water loss, and treatment satisfaction	59 AEs were reported, including gastrointestinal issues, dizziness, cataract, and upper respiratory infection

These results are supported by another retrospective cohort study in which 6 patients with NE were treated with dupilumab at standard dosing. Overall, 5/6 patients experienced a decrease in affected body surface area (≥90% improvement) throughout two years of follow-up. One patient discontinued dupilumab due to fluctuating response and the development of conjunctivitis.[11]

In another retrospective cohort study of 14 children with NE treated with dupilumab, 12/14 children experienced significant clinical improvement at a median time of 2.5 months. POEM scores, available for 5 patients, improved from a median of 23 at baseline to 2.5 at follow-up. One patient developed psoriasis, leading to dupilumab discontinuation.[10]

In a 16-week multicenter retrospective cohort study, 30 participants with NE were treated with dupilumab. The results demonstrated a significant improvement in EASI, DLQI, and visual analogue score of pruritus from baseline to week 16 (4.83, 4.03, and 1.23, respectively; $P<0.001$). One patient reported conjunctivitis.[12]

Among a retrospective cohort study evaluating 221 patients with AD treated with dupilumab (600 mg loading; 300 mg maintenance every other week), 8 patients had severe NE. Patients with NE demonstrated significant improvements in EASI, DLQI, itch-NRS, and sleep-NRS scores after 16 weeks, with these improvements persisting to week 52 (reduction percentages: 78.04%, 77.09%, 37.28%, 79.57%, respectively; $P<0.0001$). Overall, 6 patients dropped out of the study due to inadequate response (n=2), severe conjunctivitis (n=1), elevated eosinophils (n=1), severe psoriasis (n=1), and a combination of elevated eosinophils, blepharitis, and conjunctivitis (n=1).[13]

These results are further supported by case reports and case series. In a case series of 4 children with morphological variants of AD, one child diagnosed with NE received dupilumab (600 mg loading; 300 mg maintenance monthly). By week 4, the patient demonstrated great clinical improvement with EASI and IGA scores decreasing from 24.7 and 4 at baseline to 0 by week 24. This patient experienced no AEs, although a child with prurigo nodularis who was treated with dupilumab developed conjunctivitis.[14]

In one case report, a six-year-old boy had severely pruritic NE refractory to topical steroids, calcineurin inhibitors, antibiotics, and cyclosporine. After a monthly treatment with dupilumab (300 mg), the patient demonstrated substantial clinical improvement within 2 weeks, with complete clearance persisting after one year. P-NRS decreased from nine to one. No AEs were reported.[15]

The study results suggest that NE may be driven by Th2 axis hyperactivation that is susceptible to inhibition by dupilumab.[11] Consistent with this relationship, circulating Th2 lymphocyte burden has been previously correlated with NE disease activity.[16] Additionally, psoriasiform reactions were frequently reported as AEs across the studies. This trend may reflect a shared immunologic axis between psoriasis and NE, in which the Th2/Th17 mechanism of psoriasis could predispose an NE patient to psoriasiform reactions when the Th2 pathway is inhibited.[6]

Grade of recommendation: B for dupilumab for the treatment of NE based on five Level 2b retrospective cohort studies with an additional supportive Level 4 case series and case report (Table 2).

Tralokinumab

Tralokinumab is an interleukin-13 inhibitor that is FDA-approved for treating moderate-to-severe AD in patients 12 years or older.[17]

In the retrospective, single-center cohort study mentioned earlier, 59 patients with NE were enrolled who were treated with dupilumab or tralokinumab for 52 weeks. As early as week 4, participants treated with tralokinumab had significantly improved scores in EASI-75, P-NRS, SD-NRS, DLQI, ADCT, and POEM, with consistent improvement until week 52 ($P<0.001$). Tralokinumab was discontinued in 5 patients due to inefficacy (n=2), injection-site reaction (n=1), and new-onset psoriasis (n=2). Similar to dupilumab, the patients' positive results after treatment with tralokinumab indicate that NE may be driven by Th2 pathways, which tralokinumab modulates.

Grade of recommendation: B for tralokinumab for the treatment of NE based on one Level 2b retrospective cohort study (Table 2).

TABLE 2.

Level of Evidence and Grades of Recommendation According to Oxford Center for Evidence-based Medicine[22]

Level of Evidence	Grades of Recommendation
1a. Systematic review of RCTs 1b. Individual RCT 2a. Systematic review of cohort studies 2b. Individual cohort study (including low-quality RCT) 3a. Systematic review of case-control studies 3b. Individual case-control study 4. Case series 5. Case reports, expert opinion, bench research	A. Consistent level 1 studies B. Consistent level 2 or 3 studies or extrapolations from level 1 studies C. Level 4 studies or extrapolations from level 2 or 3 studies D. Level 5 evidence or troubling inconsistent or inconclusive studies of any level

RCT: Randomized controlled trial

Grade of Recommendation: C Supporting Treatment of Nummular Eczema

Roflumilast

Roflumilast is an FDA-approved treatment for plaque psoriasis, atopic dermatitis, and seborrheic dermatitis.[18] Roflumilast is a selective inhibitor of PDE4, an intracellular enzyme that hydrolyzes cyclic adenosine monophosphate, thereby increasing the levels of inflammatory cytokines involved in various inflammatory skin diseases.[9]

We identified one case report that evaluated the efficacy of oral roflumilast (500 µg daily) in a 69-year-old woman with NE refractory to topical steroids, ultraviolet B (UVB), methotrexate, and azathioprine. The patient experienced marked clinical improvement within 2 weeks. She demonstrated complete clearance at 4 weeks and maintained remission at 24 weeks of follow-up. Her AEs included 6 kg weight loss, gastrointestinal issues, and headaches.[9]

Patients with atopic disease are known to exhibit increased PDE4 activity relative to healthy skin and have dysregulated nucleotide metabolism.[9] While the results support the use of roflumilast in treating NE by modulating the PDE4 pathway, RCTs are needed to confirm its safety and efficacy.

Grade of recommendation: C for oral roflumilast for the treatment of NE based on one Level 4 case report (Table 2).

Delgocitinib

Delgocitinib is FDA-approved for the treatment of moderate-to-severe chronic hand eczema.[19] Delgocitinib is a pan-JAK inhibitor that modulates multiple inflammatory pathways and reduces cytokine signaling associated with pruritus, including IL-4, IL-13, and IL-31.[20]

Our search identified a case report of a 4-year-old girl with pruritic, severe NE unresponsive to topical steroids, antihistamines, and antimicrobials. After 8 weeks of treatment with narrowband ultraviolet B (NB-UVB) once weekly (400mJ/cm2) and topical delgocitinib twice daily, the patient's NE improved remarkably, from an elevated, erythematous, brown lesion to a flat light-brown lesion.[21] Although this case suggests a favorable response in NE, the clinical improvement cannot be definitively attributed to delgocitinib, given its concomitant use with NB-UVB phototherapy.

Grade of recommendation: C for delgocitinib in combination with NB-UVB for the treatment of NE based on one Level 4 case report (Table 2).

Grade of Recommendation: B Against Treatment of Nummular Eczema

Apremilast

Apremilast is a selective PDE4 inhibitor that is FDA-approved for the treatment of plaque psoriasis, psoriatic arthritis, and oral ulcers caused by Behcet's disease.[5]

In a 32-week randomized, double-blind, placebo-controlled phase IIb study, the safety and efficacy of apremilast (30 mg twice daily) compared with a matched placebo were investigated in 31 patients with NE. One patient treated with apremilast and 4 patients receiving the placebo demonstrated improvement in Physician's Global Assessment (PGA). By week 16 and 32, there were no differences between apremilast and placebo in PGA improvement, EASI50, biopsy skin inflammation, quality of life, pruritus, transepidermal water loss, or treatment satisfaction. The authors concluded that there is no evidence for the use of apremilast in treating NE. Overall, 59 AEs were reported, including gastrointestinal issues, dizziness, cataract, and upper respiratory infection.[5]

Considering apremilast's lack of efficacy in treating NE and its FDA approval for psoriasis, a Th17-driven disease, the results suggest that Th17-mediated inflammation is unlikely to be the predominant mechanistic pathway in NE.[5]

Grade of recommendation: B against the use of apremilast for the treatment of NE based on one Level 2b randomized, double-blind, placebo-controlled phase IIb study showing no superiority to placebo (Table 2).

Clinical Recommendations

Current evidence supports the use of dupilumab and tralokinumab for patients with NE. Dupilumab warrants a Grade B recommendation for NE, supported by five Level 2b retrospective cohort studies and additional Level 4 case reports, demonstrating rapid and sustained improvement in EASI, pruritus, sleep disturbance, and quality of life in adults and children. Tralokinumab similarly received a Grade B recommendation based on one Level 2b retrospective cohort, with comparable improvements in disease severity scores. Oral roflumilast and topical delgocitinib (in combination with NB-UVB) each received a Grade C recommendation. While demonstrating marked clinical improvement, their evidence is limited to single Level 4 case reports, constrained by small sample sizes and, in the case of delgocitinib, confounded by concomitant phototherapy. In contrast, apremilast received a Grade B recommendation against use in NE, given a Level 2b randomized, double-blind, placebo-controlled phase IIb trial demonstrating no superiority to placebo for any of the outcomes.

AEs across studies were generally consistent with known medication safety profiles. Collectively, these data support dupilumab and tralokinumab as preferred options for NE, with roflumilast and delgocitinib reserved for highly selected cases and apremilast not recommended outside of research settings.

CONCLUSION

Biologics and small-molecule inhibitors targeting Th2, JAK, and PDE4 pathways represent emerging therapeutic options for patients with NE. Dupilumab and tralokinumab demonstrated the most consistent clinical benefit, supporting their off-label use with a Grade B recommendation, while roflumilast and delgocitinib (with NB-UVB) showed promising but preliminary results meriting Grade C recommendations. In contrast, apremilast is not recommended for NE. Limitations of this review include small sample sizes, predominantly retrospective designs, and heterogeneous outcome measures, which constrain cross-study comparisons. High-power, randomized controlled trials with standardized endpoints and diverse patient populations are needed to define optimal therapeutic strategies for NE management.

DISCLOSURES

The authors have no conflicts of interest to disclose.

ACKNOWLEDGMENT

LJ performed the literature search and wrote the main manuscript. LJ and JS reviewed the studies independently. JS and JJ helped to edit the final manuscript. All authors reviewed and approved the final manuscript.

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*González Fernández D, Quinn C, Alhayek S, Prasad AR, Fernández Gómez L, Castaño M, Nicolaía E, Péres-Fernández A, Kilgour JM. Efficacy of a dual-serum cosmetic system in women with female pattern hair loss. J Drugs Dermatol. 2026;25(6):83251s3-83251s10. doi:10.36849/JDD.83251. Not intended to diagnose, treat, cure, or prevent any disease or medical condition.

doi:10.36849/JDD.10255

October 2026 926 Volume 25 • Issue 10

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Fundamentals of Hyperpigmentation Disorders: Causes, Concerns, and Treatment Strategies, Particularly in Skin of Color Patients

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ABSTRACT

Background: Pigmentary disorders, including hyperpigmentation, are among the most common dermatologic diagnoses in individuals with skin of color (SOC), particularly individuals with African, Asian, or Hispanic heritage, and often carry a significant quality-of-life burden. Although the evidence base has grown, gaps persist in epidemiology, in pathophysiology-driven treatment selection, and in the appropriate representation of Fitzpatrick skin types III to VI in clinical studies.

Methods: A comprehensive review of PubMed and Medline-indexed hyperpigmentation literature published between 2000 and 2026 was reviewed, with priority given to randomized controlled trials, meta-analyses, large epidemiologic series, and consensus statements.

Results: Our current understanding of hyperpigmentation has extended well beyond melanocyte hyperactivity alone. Across the major hyperpigmentation disorders, visible light acting through opsin-3 (OPN3), inflammatory and hormonal signaling, and, in melasma, basement-membrane disruption with a senescent dermal microenvironment contribute to pigment formation and treatment resistance, findings that highlight the importance of both UV radiation and visible-light photoprotection. Clinical and meta-analytic evidence supports a multimodal therapeutic approach, consistent with recent international consensus recommendations. Quality-of-life impairment is consistent across populations, a pattern that should inform counseling, while commonly used diagnostic tools and machine-learning algorithms continue to underperform in skin of color.

Discussion: Treatment of hyperpigmentation remains a multimodal therapy with the need for routine assessment of patient-reported quality of life impact.

Conclusion: Closing the evidence gap for skin of color is the next priority in treatment of hyperpigmentation and will require inclusive trial design, validated diagnostic tools, and standardized outcome measures.

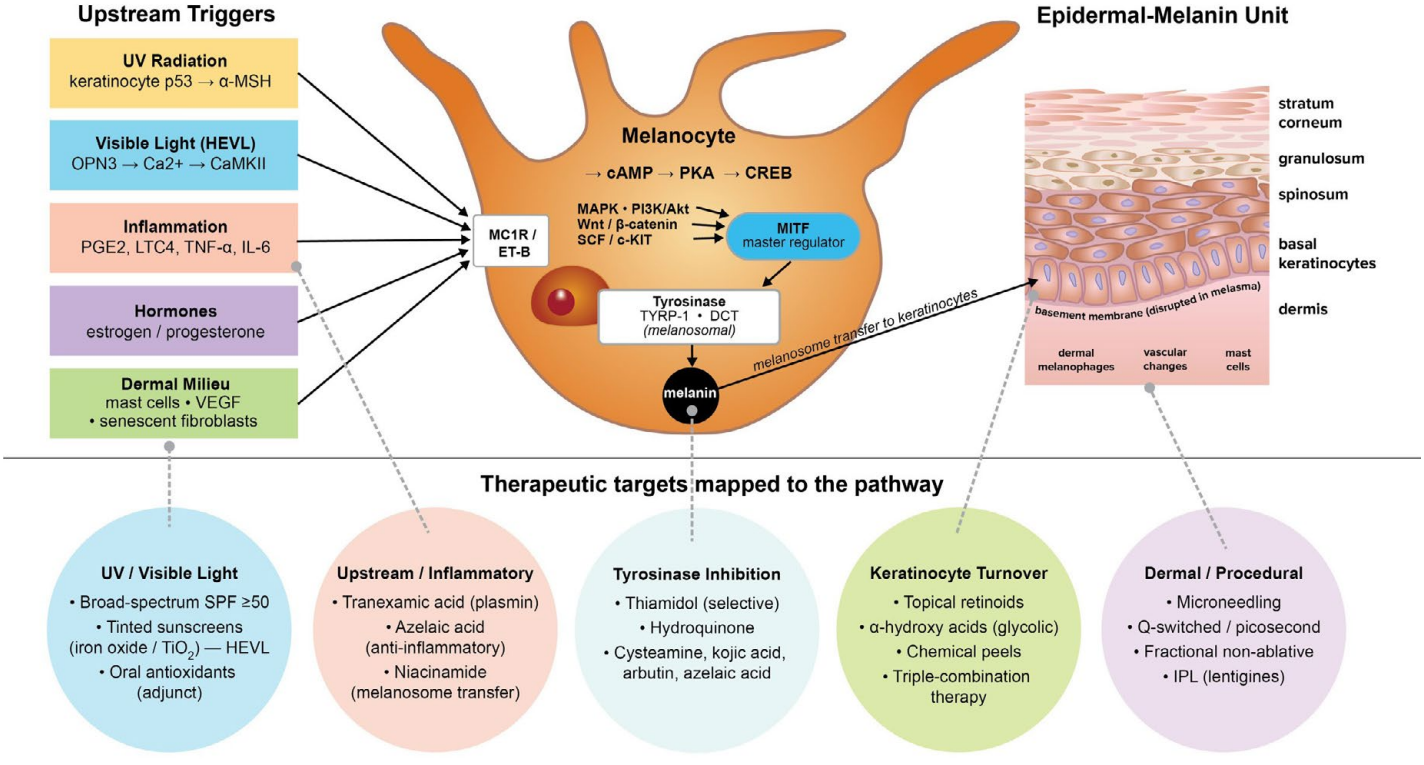
J Drugs Dermatol. 2026;25(10):926-933. doi:10.36849/JDD.10255

INTRODUCTION

Pigmentary disorders, including cutaneous hyperpigmentation, are among the most common dermatologic diagnoses in individuals with SOC, particularly individuals with African, Asian, or Hispanic heritage.[1,2] The principal hyperpigmentation conditions include melasma, post-inflammatory hyperpigmentation (PIH), solar lentigines, drug-induced and infectious pigmentary changes, maturational dyschromia, and acquired dermal macular hyperpigmentation (ADMH). In a cross-sectional analysis of 41,283 patients, melasma was significantly more prevalent in Asian and Hispanic populations, and was strongly comorbid with rosacea and atopic dermatitis.[3]

For the clinician, the central difficulty is rarely diagnosis; it is the management of a chronic and relapsing condition, the disproportionate burden carried by patients with deeply pigmented skin, and the gap between the populations enrolled in clinical trials and those encountered in practice. This review summarizes the state-of-the-science on hyperpigmentation, with a particular focus on SOC patients, that should help guide treatment approaches.

FIGURE 1. Melanogenesis and therapeutic targets. Upstream triggers, including UV, visible light acting through OPN3, inflammation, hormones, and the dermal milieu, converge on the melanocyte to activate MITF through the α-melanocyte-stimulating hormone (α-MSH)/melanocortin-1 receptor (MC1R)/cyclic AMP, Wnt/β-catenin, SCF/c-KIT, MAPK, and PI3K/Akt cascades. MITF in turn drives expression of tyrosinase, TYRP-1, and DCT. The lower panel maps the major therapeutic classes to their points of intervention: 1) photoprotection; 2) upstream and inflammatory modulators (TXA, azelaic acid, niacinamide); 3) tyrosinase inhibitors (thiamidol, hydroquinone, cysteamine, kojic acid, arbutin); 4) keratinocyte-turnover agents (retinoids, α-hydroxy acids, triple combination); and 5) procedural and dermal interventions.[4,5,32,35,42-45]



α-MSH, alpha-melanocyte-stimulating hormone; ATK, protein kinase B; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; cAMP, cyclic adenosine monophosphate; SCF, Skp, Cullin, F-box containing complex; c-KIT, CD117 KIT proto-oncogene receptor tyrosine kinase; CREB, cAMP-response-element-binding protein; DCT, dopachrome tautomerase; ET-B, endothelin receptor type B; HEVL, high-energy visible light; IL-6, interleukin-6; IPL, intense pulsed light; LTC4, leukotriene C4; MAPK, mitogen-activated protein kinase; MC1R, melanocortin-1 receptor; MIFT, microphthalmia-associated transcription factor; OPN3, Opsin-3; PGE2, prostaglandin E2; PKA — protein kinase A; PI3K, phosphoinositide 3-kinase; SPF, sun protection factor; TNF-α, tumor necrosis factor alpha; TXA, tranexamic acid; TYRP-1, tyrosinase-related protein 1; VEGF, vascular endothelial growth factor.

MATERIALS AND METHODS

The authors conducted a comprehensive review of the literature, searching PubMed and MEDLINE for peer-reviewed, English-language articles published between 2000 and 2026, with an emphasis on those appearing from 2015 onward. Search terms combined Medical Subject Headings (MeSH) and free-text descriptors for the hyperpigmentation subtypes, melanogenesis, skin of color, validated outcome instruments, and therapeutics. Randomized controlled trials (RCTs), systematic reviews and meta-analyses, consensus statements, and large epidemiologic studies were prioritized.

Epidemiology and Pathophysiology

Three mechanistic developments over the past decade have reshaped how health care providers should approach hyperpigmentation (Figure 1). The first concerns visible light. It is now clear that visible light, and in particular the high-energy short-wavelength (blue) band, drives sustained pigmentation in Fitzpatrick skin types (FSTs) III to VI by acting on opsin-3 (OPN3) on melanocytes, triggering a calcium-dependent CAMKII/CREB/MAPK cascade that phosphorylates microphthalmia-associated transcription factor (MITF) and produces a stable tyrosinase/TYRP-1 complex.[4] Because broad-spectrum sunscreens protect only against ultraviolet (UVA/UVB) radiation alone, use of high sun protection factor (SPF) sunscreen alone is insufficient in darker skin types (FST III-VI); thus, counseling should explicitly address visible-light exposure particularly for SOC patients.

The second development is the recognition that the pathology of hyperpigmentation, and of melasma in particular, extends well beyond melanocyte hyperactivity. Basement-membrane disruption with pendulous melanocytes and melanin incontinence, solar elastosis, mast-cell accumulation, senescent fibroblasts, and elevated vascular endothelial growth factor (VEGF) expression are now recognized as contributing features.[5,6] These findings help to explain why dermal and mixed-pattern disease tends to be chronic and why rebound is common after procedures, and they provide the rationale for combining several treatment modalities to achieve success.

The third development is a clearer understanding of how inflammatory and hormonal triggers operate. Keratinocyte-derived prostaglandins, leukotrienes, and cytokines, including interleukin-1, interleukin-6, tumor necrosis factor-α, stem cell factor (SCF), and interleukin-33, drive PIH, whereas estrogen and progesterone receptors on melanocytes mediate the hormonal susceptibility characteristic of melasma.[6] In addition, epigenetic regulation of tyrosinase, TYRP1, dopachrome tautomerase (DCT), and MITF through DNA methylation, histone acetylation, and non-coding RNAs offers a plausible explanation for treatment resistance.[7] Taken together, these advances support a layered approach that addresses upstream signaling, the melanogenic enzymatic apparatus, and the dermal contributors that topical therapy alone may not reach.

Clinical Types: Focus on Diagnostic and Recognition Gaps

Hyperpigmentation disorders can be organized according to etiology, distribution, depth (epidermal, dermal, or mixed), Fitzpatrick predilection, and characteristic associations (Table 1). Of these features, depth is the most consequential, because dermal and mixed pigmentation are predictably refractory to topical therapy and account for most treatment failures when they are overlooked.[5] The centrofacial pattern accounts for approximately 95% of melasma cases;[8] whereas the malar and mandibular variants are easily mistaken for poikiloderma of Civatte or ADMH and are consequently undertreated. Two categories deserve particular emphasis because they remain under-recognized, and each is readily mistaken for melasma.

Maturational dyschromia

This entity presents as ill-defined hyperpigmented patches on the lateral cheeks, temples, and forehead of middle-aged to older patients with skin of color, and it reflects the effect of cumulative ultraviolet (UV) and visible-light exposure on age-related melanocyte changes.[9,10] It is commonly misdiagnosed as melasma, which can lead to inappropriate hormonal counseling and the overuse of hydroquinone-containing regimens. Appropriate recognition and diagnosis could lead to appropriate management centered on sufficient UV radiation and visible light photoprotection.

Infectious causes of hyperpigmentation

These causes are often under-taught despite their global relevance. Visceral leishmaniasis (kala-azar) classically presents with diffuse skin darkening and may be the presenting sign in immunocompromised patients, including those with human immunodeficiency virus (HIV) coinfection.[11,12] Chikungunya infection produces characteristic centrofacial and nasal hyperpigmentation (the "chik sign"), reported in 37.5% of patients in a tertiary-care series.[13,14] Dengue fever can produce post-rash macular pigmentation.[15] Tinea versicolor, caused by *Malassezia* species, produces hyperpigmented or hypopigmented scaly trunk patches that are identifiable by yellow Wood-lamp fluorescence and potassium hydroxide examination.[16] In HIV and AIDS, generalized cutaneous hyperpigmentation may reflect antiretroviral therapy (notably zidovudine), opportunistic infection, adrenal insufficiency, or HIV itself.[11,12] In these settings,

TABLE 1.

Practical Classification of Cutaneous Hyperpigmentation Disorders

Subtype	Distribution	Depth	Fitzpatrick	Clinical Pearls / Associations
Melasma	Centrofacial (~95%); malar; mandibular face	Epidermal / dermal / mixed	III–V	Female predominance; pregnancy, oral contraceptives; UV + visible light; comorbid rosacea, atopic dermatitis
PIH	Sites of prior inflammation or injury	Epidermal > dermal	IV–VI	Acne, atopic dermatitis, procedures; persistent in deeper phototypes
Solar lentigines	Dorsal hands, face, forearms, upper chest	Epidermal	Any (rises with age)	Cumulative UV; differentiate from early lentigo maligna
Drug-induced	Diffuse, photoexposed, or mucosal	Variable	Any	Minocycline, antimalarials, amiodarone, chemotherapy; polypharmacy a risk factor
Endocrine / systemic	Diffuse or flexural	Variable	Any	Addison's disease, insulin resistance, hemochromatosis
ADMH (lichen planus pigmentosus, erythema dyschromicum perstans, Riehl's)	Face, neck, trunk	Dermal	III–VI	Lichenoid interface inflammation; concentrated in skin of color
Maturational dyschromia	Lateral cheeks, temples, forehead	Epidermal	IV–VI	Cumulative UV + visible light; age-related; often misdiagnosed as melasma
Infectious (kala-azar, chikungunya, dengue, tinea versicolor, HIV)	Diffuse (kala-azar, HIV); centrofacial / nose (chikungunya); trunk (tinea versicolor)	Epidermal ± dermal	Any (severe in skin of color)	Visceral leishmaniasis; arboviral; Malassezia; ART, opportunistic infection

ADMH, acquired dermal macular hyperpigmentation; ART, antiretroviral therapy; HIV, human immunodeficiency virus; PIH, post-inflammatory hyperpigmentation; UV, ultraviolet light.

identifying the underlying cause early, may guide overall treatment approach.

Acquired dermal macular hyperpigmentation

Acquired dermal macular hyperpigmentation (ADMH), formalized by global consensus in 2018 and reaffirmed in 2025, encompasses lichen planus pigmentosus, erythema dyschromicum perstans, idiopathic eruptive macular pigmentation, and Riehl melanosis.[17,18] These entities are concentrated in skin of color and share overlapping clinical and histopathologic features.

Impact on Quality of Life

While hyperpigmentation disorders are common, the extent and location of involvement can significantly affect quality of life (QoL), including a significant psychological burden for patients.[9] A 2022 meta-analysis of 14 studies (n = 1,398) demonstrated consistent QoL impairment across diverse melasma populations, with emotional distress and impaired social functioning predominating.[19] In a Greek case-control study, Melasma Area and Severity Index (MASI) severity correlated with both depression and Melasma Quality of Life (MELASQoL) scores, and the prevalence of anxiety was significantly elevated.[20] Furthermore, in a South African cohort of Fitzpatrick IV to VI patients, menopausal status, cheek involvement, severity, and educational level each independently predicted MELASQoL impairment, indicating that deeper pigmentation does not lessen the burden.[21]

Two findings should shape how dermatology HCPs structure their conversations with patients. First, clinical improvement in pigmentation does not reliably track patient-reported burden because MASI and MELASQoL correlate inconsistently, which indicates that objective severity and lived experience capture related but distinct dimensions.[19] A patient who reports persistent psychosocial impact despite a documented improvement in MASI is not reporting in error, and dismissing this response may lead to the lack of continued treatment adherence. Second, PIH compounds the burden of the underlying dermatosis. Acne in particular is associated with elevated anxiety, depression, and suicidal ideation;[22] and in skin of color the residual pigmentation often outlasts the primary lesions.[23] Assessing patient-reported burden at baseline and at follow-up therefore identifies the patients whose pigmentation has responded adequately but whose psychosocial burden warrants additional support.

Diagnostic Gaps in Skin of Color

The diagnostic literature for pigmentary disorders shows a consistent pattern, in that the tools dermatology HCPs rely on were validated predominantly in lighter phototypes and lose accuracy in SOC patients. Wood-lamp examination, for example, shows progressively attenuated contrast as constitutive epidermal melanin increases, which limits subtype discrimination in Fitzpatrick V to VI patients, precisely where the distinction would most influence therapy.[5,8] Dermoscopic atlases for inflammatory and pigmentary dermatoses likewise remain skewed toward lighter phototypes, with few published studies explicitly reporting Fitzpatrick IV to VI representation;[24] and for the ADMH entities, the clinical and histopathologic overlap was substantial enough to require international consensus statements to harmonize nomenclature.[17,18] Additionally, machine-learning algorithms tend to amplify these gaps.

A 2022 review documented widespread underreporting and underrepresentation of diverse skin types in machine-learning research.[25] In the absence of phototype-stratified validation, claims of equivalent algorithmic performance across skin types are unsupported, and uncorrected bias risks encoding historical underrepresentation into artificial intelligent (AI)-driven algorithms.

Therapeutic Approaches

Across the hyperpigmentation evidence base, the multimodal approach remains the most consistent and effective approach. Expert consensus statements developed over the past decade,[17,18,26-28] 2 systematic reviews,[29,30] and a substantial body of randomized controlled trial (RCT) and meta-analytic data converge on the same core principles, namely foundational photoprotection that includes visible light, multimodal topical therapy as first line, escalation to oral and procedural options for refractory disease, and structured maintenance. The 2025 global modified-Delphi consensus offers a contemporary synthesis;[18] but the same principles are supported by parallel regional and international expert opinion and by the primary literature.

Photoprotection

Photoprotection is foundational across all melanin hyperpigmentation disorders. The visible-light pathway mediated by opsin-3 (OPN3) provides the mechanistic rationale,[4] and tinted sunscreens containing iron oxides or pigmentary titanium dioxide are the only formulations supported by randomized data showing prevention of hyperpigmentation induced by visible light.[31] Because visible light drives pigmentation in part through the generation of reactive oxygen and nitrogen species, sunscreens that combine visible-light-attenuating pigments with topical antioxidants offer a complementary mechanism, and early clinical studies indicate that antioxidant-containing formulations reduce visible-light-induced erythema and pigmentation and may limit worsening of existing pigmentary disorders.[32] Patients with skin of color therefore require formulations that both absorb visible light and counter the effects of reactive species, because a non-tinted broad-spectrum sunscreen alone, however high its SPF, is mechanistically insufficient.

Topical therapy

Topical therapy is itself multimodal because no single agent addresses the multiple pathways that contribute to hyperpigmentation. Two systematic reviews concluded that

TABLE 2.

Principal Topical and Oral Therapies for Hyperpigmentation

Agent	Mechanism	Indication	Evidence
Hydroquinone	Tyrosinase inhibition	Melasma, PIH, lentigines	Grade A; ochronosis risk; not for maintenance
Triple combination (hydroquinone + tretinoin + fluocinolone)	Multi-pathway	Moderate-to-severe melasma, first line	Grade A; rebound risk limits maintenance
Non-hydroquinone triple combination	Multi-pathway	Mild melasma, first line	Consensus[18]
Azelaic acid	Tyrosinase inhibition, anti-inflammatory	Melasma, PIH; pregnancy	Grade A; pregnancy-safe
Kojic acid	Tyrosinase inhibition	Melasma, PIH; adjunct	Grade A adjunct
Niacinamide	Inhibits melanosome transfer	Melasma, PIH; maintenance	Adjunctive evidence; maintenance role
Retinoids (tretinoin, adapalene)	Keratinocyte turnover	Epidermal melasma, PIH, photodamage	First-line + maintenance for photodamage
Cysteamine	Antioxidant, tyrosinase inhibition	Melasma second-line, maintenance	Consensus[1]
Thiamidol	Selective human tyrosinase inhibition	Melasma, acne-PIH, periorbital, flexural; maintenance	Non-inferior to hydroquinone 4% (Lima);[33] 24-wk RCT (Roggenkamp)[34]
Topical TXA	Plasmin inhibition	Melasma first-line; PIH	Consensus first-line mild melasma
Oral TXA	Plasmin inhibition	Moderate-to-severe / refractory melasma	Grade A meta-analysis[35]
Intradermal TXA / microneedling-delivered TXA	Plasmin inhibition	Moderate-to-severe melasma	Superior MASI vs. oral/topical; meta-analysis[36]
Arbutin	Tyrosinase inhibition	Mild melasma first-line; periorbital	Consensus[18]
Polypodium leucotomos (oral)	Antioxidant, photoprotective adjunct	Melasma adjunct; HEVL protection	Adjunctive evidence[43]

HEVL, high energy visible light; MASI, Melasma Area and Severity Index; PIH, post-inflammatory hyperpigmentation; RCT, randomized controlled trial; TXA, tranexamic acid.

combinations of tyrosinase inhibitors (thiamidol, hydroquinone, kojic acid, arbutin), retinoids, azelaic acid, antioxidants, niacinamide, and topical tranexamic acid (TXA) outperform monotherapy.[29,30] The principal topical and oral agents, with their indications and supporting evidence, are summarized in Table 2. Head-to-head trial data support particular agents, in that a 90-day evaluator-blinded RCT demonstrated non-inferior MASI reduction with thiamidol compared with hydroquinone 4% (43% vs 33%),[33] and a 24-week vehicle-controlled RCT confirmed the efficacy of thiamidol in moderate-to-severe Fitzpatrick III to V melasma.[34] Use of any topical agent(s) as first line therapy should be monitored for adverse events, and adjusted accordingly or by patient preference with appropriate consultation.

Tranexamic acid

Tranexamic acid (TXA) is a valuable adjunct that can be delivered via several routes. A 2021 meta-analysis of 24 RCTs found that oral TXA 250 mg twice daily produced significant reductions in MASI and modified MASI (mMASI) without serious adverse events,[35] and a 2024 meta-analysis of 17 RCTs found that intradermal injection and microneedling-delivered TXA outperformed the oral and topical routes on MASI endpoints, although oral administration yielded greater patient satisfaction.[36] A 2024 Delphi consensus from the Indian Pigmentary Disorders Society describes prescribing practices for oral TXA, including pretreatment screening for thromboembolic risk and quarterly coagulation monitoring.[26] Together, these data position TXA as a valuable treatment option with appropriate monitoring.

Procedural therapy

Procedural therapy occupies a defined role in refractory disease and in mixed or dermal disease, with phototype-specific considerations that guide selection (Table 3). An open-label RCT of intense pulsed light added to a stable fixed-dose triple combination produced approximately 49% MASI reduction at month 6 and 45% at month 12 compared with triple combination alone.[37] For solar lentigines, a 2025 systematic review identified pigment-specific lasers (Q-switched and picosecond) and intense pulsed light as first-line, and noted that picosecond systems produce less rebound PIH than Q-switched platforms in darker phototypes.[38] For acne-associated PIH, priming the skin with a lightening agent and avoiding perioperative retinoids reduces iatrogenic pigmentation in Fitzpatrick V to VI patients.[23]

TABLE 3.

Procedural Interventions by Indication and Fitzpatrick Considerations

Procedure	Strongest Indication	Evidence	Cautions in Fitzpatrick IV–VI
Superficial peels (glycolic, salicylic, mandelic)	Melasma, PIH	Moderate; adjunct to topicals	Start low concentration; PIH risk with overuse
Jessner / low-concentration TCA peel	Melasma, PIH	Moderate	Experienced operators only
Microneedling ± topical TXA	Dermal/mixed melasma	Strong for dermal variant[36]	Generally safe across phototypes
Q-switched Nd:YAG (low fluence)	Refractory melasma; non-acne PIH	Variable; recurrence common	Multiple passes increase PIH and rebound risk
Picosecond laser	Solar lentigines; refractory melasma	Strong for lentigines[38]	Lower PIH than Q-switched in lentigines
Intense pulsed light	Solar lentigines; freckles; refractory melasma (with triple combo)	Strong (74.6–90%);[38] ~49% MASI reduction at 6 mo combined with triple combo[36]	Caution in deeper phototypes
Cryotherapy	Solar lentigines	Moderate	Avoid in Fitzpatrick IV–VI (high PIH risk)

MASI, Melasma Area and Severity Index; PIH, post-inflammatory hyperpigmentation; TCA, trichloroacetic acid; TXA, tranexamic acid; YAG, yttrium aluminum garnet.

Maintenance and special situations

Three principles unify the therapeutic evidence and should be included in any multimodal treatment algorithm. First, maintenance differs from active treatment, and long-term use of a hydroquinone-based approach should be limited and/or heavily monitored due to cumulative tolerability and rebound concerns. Given this, use of non-hydroquinone agents, including antioxidants, kojic acid, thiamidol, retinoids, TXA, arbutin, azelaic acid, and niacinamide, should be considered for long term maintenance.[17,18,26,28,30] Second, intravenous glutathione is not recommended at any line, because the efficacy data are insufficient and safety concerns remain.[18] Third, the pregnancy-safe options are photoprotection, azelaic acid, and glycolic acid.[18,27] For hyperpigmentation associated with infection, treatment of the underlying infection, whether anti-leishmanial, anti-fungal, or anti-retroviral, is primary, with photoprotection and topical treatment reserved for residual pigmentation, and post-chikungunya nasal pigmentation typically resolves over months without specific therapy.[11,13,14,16]

Conclusion and Critical Gaps

Hyperpigmentation disorders fall most heavily on the patients who are least well represented in dermatologic evidence, education, and algorithm development. The literature has nonetheless advanced therapy considerably, providing head-to-head and meta-analytic support for visible-light photoprotection, multimodal topical regimens, route-stratified TXA, severity-graded escalation, and structured maintenance. The remaining gaps are concentrated in SOC, where dermoscopic atlases, machine-learning training data, validated outcome measures, and trial populations all underrepresent patients with Fitzpatrick skin types III to VI.[3,5,21,25,38-41] Closing these gaps will require inclusive trial design, phototype-stratified validation, harmonized outcome measures, and attention to patient-reported burden alongside objective severity. In the meantime, the responsibility falls to the dermatology community to apply the existing evidence with full awareness of the populations from whom it was derived, and to seek, document, and act on patient-reported burden in every consultation.

DISCLOSURES

ST has served as an investigator for Allergan Aesthetics, Concert Pharmaceuticals, Croma-Pharm GmbH, Lilly, and Pfizer; as a consultant for Arcutis, Armis, Avita Medical, Beiersdorf, Biorez Inc, BMS, Cara Therapeutics, Dior, EPI Health, Estée Lauder, Evolus Inc, Galderma, GloGetter, Hugel America, Incyte, Johnson & Johnson, L'Oréal, Lilly, Medscape, Pfizer, Piction Health, Sanofi, Scientis US, UCB, Vichy Laboratories; as a speaker for Beiersdorf, Catalyst Medical Education, CME Outfitters, DermSquared, HMP Global, LearnSkin, Medscape, and MJH Lifesciences; and as an editorial board member for Archives in Dermatologic Research, Cutis, and Practical Dermatology. She has also received royalties from McGraw-Hill.

SRD has served as a consultant, investigator, and/or advisor for AbbVie, Arcutis, Beiersdorf, Eli Lilly, Galderma, Incyte, Novartis, Pfizer, Regeneron, Sanofi, Sun Pharma, UCB, and other companies involved in dermatologic therapeutics.

CF has served as an investigator, consultant, advisory board member, and/or speaker for AbbVie, Acclaro, Aerolase, Apogee, Beiersdorf, Benev, Bubble, Crown Aesthetics, Estée Lauder, Galderma, Incyte, Johnson & Johnson, Kenvue, L'Oréal, Novartis, Pierre Fabre, Procter & Gamble, Reframe Beauty, Revance, Sun Pharma, Veradermics, Viking Therapeutics, Xtresse, and Zenzema.

NE has served as a consultant, advisory board member, and/or speaker for AbbVie, Allergan, Beiersdorf, Canfield, Dior, Eli Lilly, Incyte, Janssen, Kao USA, Kenvue, La Roche-Posay, L'Oréal, McGraw-Hill, Medscape, Pfizer, Sanofi, Skinceuticals, Takeda, Teva, and Veradermics. She has grant funding from Eli Lilly and Pfizer, has received royalties from McGraw-Hill and has stock options in VisualDx.

PEG has served as an investigator and/or consultant for Allergan, BOD Clinuvel, Clinuvel, Incyte, Johnson & Johnson, L'Oréal, Merck, Pfizer, SkinBetterScience, and Versicolor Technologies.

AA has served as a consultant, advisory board member, investigator, and/or speaker for AbbVie, Aerolase, Allergan, Almirall, Alphyn, Alumis, Amgen, Apogee BioPharm, Arcutis, BauschHealth, Beiersdorf, Inc., Boehringer Ingelheim, Botanix Pharmaceuticals, Bristol Myers Squibb, Canfield Scientific, Castle Biosciences, Caudalie, Dermavant, DermSquared, Eli Lilly, Galderma, Genentech, HairDays, Incyte, Janssen Scientific Affairs, Johnson & Johnson, LEO Pharma, L'Oréal, Novartis, Oruka Therapeutics, Pfizer, RBC Consultants, Regeneron, Sanofi, Sanofi Genzyme, Sanofi/Regeneron, Scientis, Symrise, Takeda, UCB, and Veradermics Inc. He has also received royalties from Elsevier, Springer, UpToDate, Inc. (Wolters Kluwer Health), and Wiley-Blackwell; as well as equipment from Aerolase.

Funding Source: The publication of this manuscript was supported by Beiersdorf, Inc.

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JOURNAL OF DRUGS IN DERMATOLOGY
JDD
DRUGS • DEVICES • METHODS

"PLEASE SIR, I WANT SOME MORE:"

WHEN RESCUE BECOMES ROUTINE WITH PREDNISONE IN IBD CARE



HOST
Dr. Adam Friedman, MD, FAAD



GUEST
Dr. Adelina Hung

For decades, corticosteroids have been the gastrointestinal equivalent of duct tape: they fix almost everything, at least long enough to convince us the job is done. But as every homeowner eventually learns, duct tape isn't a long term structural solution…which is why I wish I still lived in an apartment.

In this episode of the JDD Podcast: Corticosteroid Stewardship Series, Dr. Adam Friedman welcomes Dr. Adelina Hung, a board-certified gastroenterologist, hepatologist, and founder and director of the Inflammatory Bowel Disease Program and MASH Clinic at Sinai Health System in Chicago. Together, Drs. Friedman and Hung explore why corticosteroid stewardship has become just as essential in gastroenterology as it is in dermatology. They examine how repeated corticosteroid exposure quietly accumulates across specialties, why the true burden of toxicity often goes unrecognized, and how today's expanding arsenal of steroid-sparing therapies is reshaping clinical decision making. The discussion also tackles the difficult balance between rapidly controlling disease activity and avoiding the long term consequences of repeated steroid use, while highlighting the importance of patient education, multidisciplinary communication, and ensuring that access barriers do not become the default indication for another prescription. From cumulative adverse effects and patient counseling to multidisciplinary collaboration and health equity, this conversation challenges the longstanding mindset that another course of prednisone is simply part of doing business. All in, the biggest complication of corticosteroids isn't the first prescription, it's losing count of all the ones that came before.

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This podcast is funded by Arcutis Therapeutics

doi:10.36849/JDD.10029

October 2026 935 Volume 25 • Issue 10

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

SAIGE III: The Role of Environmental Factors in the Development and Severity of Atopic Dermatitis in Young Children

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ABSTRACT

Background: Atopic dermatitis (AD) often manifests in infancy or early childhood, with significant impacts on quality of life and potential persistence into adulthood. Environmental factors are key contributors to pruritus, barrier dysfunction, and inflammation associated with AD.

Methods: A panel of 7 pediatric dermatology experts employed a modified Delphi process, including a face-to-face meeting and online follow-up, to evaluate current evidence and formulate consensus recommendations for managing pediatric AD.

Results: The panel identified environmental factors that affect skin barrier function and contribute to the development and severity of pediatric AD. Consensus recommendations emphasize minimizing environmental exposures and highlight strategies to reduce skin barrier disruption. Early and continuous use of gentle, non-alkaline cleansers and ceramide-containing moisturizers, initiated from birth, may help mitigate AD risk and severity, particularly in high-risk children.

Conclusions: Recognizing and addressing environmental factors is an important component of pediatric AD management. Addressing modifiable environmental factors and initiating early barrier-supportive skincare, including ceramide-containing moisturizers, represents a practical approach to reducing disease severity and flare development. These findings highlight the importance of clinician education to improve awareness of environmental risk factors and effective mitigation strategies.

J Drugs Dermatol. 2026;25(10):935-941. doi:10.36849/JDD.10029

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin condition that typically begins in infancy, peaks in early childhood, and persists into adulthood.[1,2] Clinical features of pediatric AD include a relapsing course with eczematous lesions, xerosis, intense pruritus, and a genetic predisposition to atopy.[1] AD affects up to 20% of the pediatric population, and prevalence rates are expected to continue increasing, with published prevalence rates likely an underestimation.[1,3] Pediatric AD significantly impacts affected children and caregivers and has been associated with an increased risk of attention deficit hyperactivity disorder (ADHD).[1,4] The early disease onset and significant patient burden highlight the importance of early prevention and management strategies.

AD pathophysiology involves a complex interplay of factors that affect skin barrier function, including *Staphylococcus aureus*, immunological, genetic, and environmental (SAIGE) factors. Variability in the clinical presentation of pediatric AD reflects the complex SAIGE mechanisms underlying the disease.[1] In addition to their role in disease development, environmental exposures may exacerbate AD by interacting with other pathogenic pathways.[1]

The SAIGE factors project seeks to mitigate AD by understanding and addressing (when possible) the SAIGE risk factors. This manuscript focuses on environmental factors that contribute to skin barrier dysfunction and AD development, including (1) climate (UV radiation, latitude, humidity) (2) air pollutants (tobacco smoke exposure, urban living, indoor, outdoor) (3) allergic sensitization (skin dysbiosis, antibiotic use) (4) water (increased hardness) (5) skincare (gentle cleansers and moisturizers).

MATERIALS AND METHODS

The SAIGE I publication[1] reviewed these factors and the role skincare plays in mitigating pediatric AD, and the SAIGE II publication reviewed the role of *S. aureus* in the development of AD. The current manuscript focuses on environmental factors affecting the development of pediatric AD and on the potential role of ceramide-containing skincare in influencing the impact of these factors.

Literature Review

This project used a modified Delphi process comprising face-to-face expert panel discussions and online follow-up. AA and HA conducted a systematic literature review of English-language publications before the panel meeting, using PubMed and Google Scholar as secondary sources. The searches addressed SAIGE factors in pediatric AD, focusing on environmental factors influencing AD development. Searches were limited to the following categories: climate (UV radiation, latitude, humidity), air pollutants (tobacco smoke exposure, urban living, indoor, outdoor), allergic sensitization (skin dysbiosis, antibiotic use), water (increased hardness), and skincare (gentle cleansers and moisturizers).

The searches encompassed clinical studies, algorithms, consensus papers, guidelines, meta-analyses, review papers, and systematic reviews from 2010 to 20th January 2025. The literature search was based on 2 key questions:

1. What is known about AD development in neonates, infants, and children influenced by SAIGE factors, focusing on environmental-driven exacerbation of AD compromising skin barrier function?
2. What is the role of skin care and ceramide-containing skincare from birth in addressing SAIGE factors, focusing on environmental factors attenuating pediatric AD and promoting a healthy skin barrier?

TABLE 1.

Systematic Literature Review Search Terms
Search Terms
Pediatric/childhood AD AND epidermal barrier dysfunction OR UV radiation OR latitude OR humidity OR tobacco smoke exposure OR urban living OR air pollution indoor/outdoor OR water pH OR diet OR in utero stress (maternal anxiety, depression, medication, substance abuse, smoking).
Pediatric/childhood AD AND Prevention OR attenuation OR treatment OR maintenance AND prescription OR adjunctive OR skincare OR moisturizer OR emollient OR ceramide

Search terms are provided in Table 1. Abstracts and then full articles were evaluated for inclusion and categorized by publication type (Figure 1). Each clinical publication that included skincare was graded by consensus of the reviewers, and any discrepancies were resolved through discussion. The reviewers (AA, HA) assigned a level of evidence to each treatment (A, B, C, and 1-4) using the established criteria. Publications in a language other than English, and those not addressing pediatric patients, topical treatments, or environmental factors that exacerbate AD, were excluded.

Role of the Panel

An expert panel of 7 pediatric dermatologists with extensive experience treating pediatric patients convened on February 7, 2025, in Miami, Florida. They reviewed and discussed the literature to identify the role of environmental factors influencing AD development.

During the meeting, advisors divided into 3 groups. The systematic literature search results informed 18 draft statements, and coupled with the panel's opinion and experience, advisors agreed (consensus ≥80% of the panel) on 6 statements supporting healthcare providers who treat pediatric patients with AD. The voting (consensus ≥80% of the panel) results were: statements 1 to 3 and 5: N=7 [100%]; and statements 4 and 6: N=6/7 [88%].

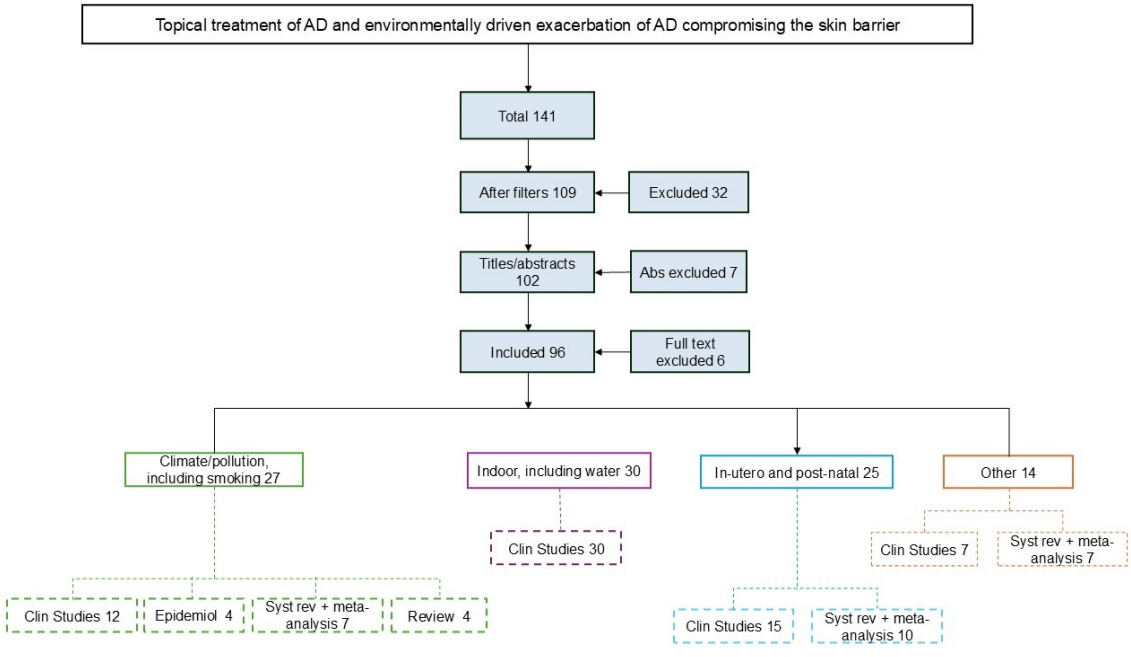
RESULTS

The consensus statements were developed from draft statements fine-tuned in a workshop and serve as the basis for the manuscript on the environmental factors that contribute to pediatric AD and the role of skincare in mitigating them.

Statement 1: *The worldwide prevalence of AD has dramatically increased over the last 50 years and likely reflects a complex interplay between genetic and immunologic predisposing factors and environmental triggers that damage the skin barrier.*

While the increasing prevalence of AD likely stems from a complex interplay between various factors, the increasing incidence in industrialized countries suggests that environmental triggers are key drivers of this trend.[5] Recent studies have found

FIGURE 1. Results of the literature searches on topical treatment of atopic dermatitis and environmental factors exacerbating atopic dermatitis.



Excluded: Publication language other than English, not including pediatric patients, topical treatment, or environmental factors exacerbating AD.

an association between urbanization and pediatric AD, as well as evidence that climate and climate change influence the concentration of air pollutants.[5,6,7] Factors like ultraviolet (UV) exposure also play a role, as regions with a higher UV index report lower rates of pediatric AD.[8,9]

The significant impact of environmental factors is linked to the compromised skin barrier characteristic of AD – including decreased lipid content – such as ceramides. Barrier dysfunction increases permeability to environmental allergens and irritants, and elicits greater epidermal inflammatory responses in patients with AD. Common environmental factors that contribute to AD exacerbation include air pollutants, environmental irritants, seasonal changes, temperature variation, and microbial exposures.[10]

Given the role of skin barrier dysfunction, early interventions aimed at supporting the skin barrier may promote skin health. Applied from birth onward, gentle cleansers and lipid-containing moisturizers may help maintain the skin barrier, thereby mitigating the onset and severity of AD in predisposed infants.[11–13]

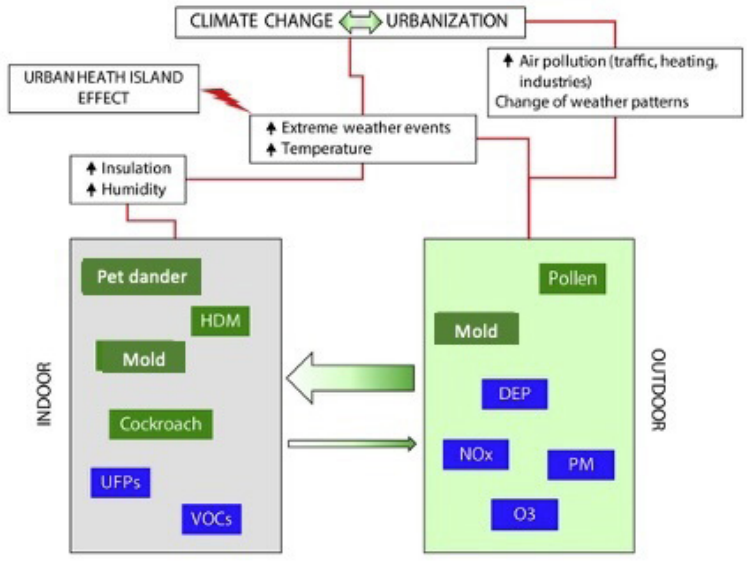
Statement 2: *Potentially modifiable environmental factors that may impact the skin barrier and exacerbate AD flares include the changing climate, urbanization, air pollutants, allergic sensitization, hard water, and poor skincare.*

Environmental variables play a significant role in the development and severity of AD (Figure 2).[5] Macro-environmental exposures associated with urbanization, air pollution, and climate change have been linked to increased risk of AD. Traffic-related air pollution, especially particulate matter <2.5 µm (PM 2.5) and nitrogen dioxide (NO_2), has been associated with increased incidence and frequency of AD.[5] In children, the odds of developing AD rise with proximity to a high-traffic road, supporting the link between urbanization and AD prevalence.[5] In addition, exposure to specific air pollutants, including NO_2, SO_2, and SO_3, has been associated with higher odds of pediatric AD (Table 2).[6]

Climate and climate change further impact AD by affecting the sources, emissions, and concentrations of aeroallergens and air pollutants, and potentially increasing the number of patients with AD.[7] Climate also influences the prevalence of pediatric AD independently of pollution. Lower AD prevalence was found in areas with higher relative humidity, higher UV index, higher mean temperatures, lower precipitation, and less indoor heating.[5]

Beyond these macro-environmental factors, everyday environmental exposures also impact AD risk and severity. While fragrances are highly prevalent in today's world, they have been shown to increase inflammatory responses in individuals with AD.[10] Females have been shown to be more

FIGURE 2. Connection between various environmental factors and atopic dermatitis development.



HDM, house dust mite; NOx, nitrogen oxides: UFPs, ultrafine particles; VOCs, volatile organic compounds; PM, particulate matter; DEPs, diesel exhaust particles; 03, ozone.
Reproduced with permission from Cecchi, Lorenzo, et al. External exposome and allergic respiratory and skin diseases. *J Allergy Clin Immunol.* 2018;141(3):846-857.

TABLE 2.

AD Air Pollution Meta-Analysis a Systematic Reviews	
Subject	**Reference**
Air pollution and global healthcare use for AD: A systematic review.	Fadadu RP et al. *J Eur Acad Dermatol Venereol.* 2023 Oct;37(10):1958-1970.
Child asthma tied to specific urban air pollutants.	Larkin HD. *JAMA.* 2023;329(5):363. doi:10.1001/jama.2022.24493
Maternal tobacco exposure during pregnancy and atopic dermatitis in offspring: A systematic review and meta-analysis.	Chao L et al. *J Eur Acad Dermatol Venereol.* 2024 Oct;38(10):1947-1953.
Smoke exposure and childhood atopic eczema and food allergy: A systematic review and meta-analysis.	Lau HX et al. *Pediatr Allergy Immunol.* 2023 Aug;34(8):e14010.
The prenatal and postnatal effects of air pollution on asthma in children with AD.	Chen H et al. *Pediatr Pulmonol.* 2022 Nov;57(11):2724-2734.
The relationship between outdoor air pollutants and AD of adults: A systematic review and meta-analysis.	Chen H et al. Asian Pacific *J Allergy Immunol.* 40 (2021): 295–307
AD is an environmental disease.	Luschkova D et al. *Allergol Select 5.* (2021): 244–250.
the role of photoprotection in optimizing the treatment of ad.	Piquero-Casals J et al. *Dermatol Ther (Heidelb).* 2021 Apr;11(2):315-325.
Association of atopic dermatitis with smoking: A systematic review and meta-analysis.	Kantor R et al. *J Am Acad Dermatol.* 2016 Dec;75(6):1119-1125.e1.
Is there a rural/urban gradient in the prevalence of eczema? A systematic review.	Schram ME et al. *Br J Dermatol.* 2010;162:964–973.

AD, Atopic dermatitis (AD).

susceptible to AD reactions towards fragrances than males, and younger populations also tend to have higher rates of fragrance-triggered AD compared with older populations.[10] Similarly, harsh detergents, increasingly present in everyday products, can be irritating to individuals with AD. Repeated exposure may further irritate the skin barrier and promote microbial imbalance, increasing vulnerability to allergic sensitization.

Water quality represents another modifiable factor. Higher AD prevalence has been reported in areas with hard water, particularly among infants and school-aged children. In these settings, minimizing exposure to hard water (eg, via shower/faucet filters) may be beneficial.[14] In addition, poor skincare can exacerbate barrier dysfunction and contribute to ongoing inflammation and sensitization. Individuals with AD benefit from appropriate skincare that supports barrier repair and improves AD symptoms.[2]

TABLE 3.

Indoor Pollution Clinical Studies	
Subject	**Reference**
Effects of residential environment and lifestyle on atopic eczema among preschool children in Shenzhen, China.	Liu Y et al. *Front Public Health* 10 (2022).
Household environmental microbiota influences early-life eczema development.	Ta LDH et al. *Environ Microbiol* 23 (2021): 7710–7722.
Sources of indoor particulate matter (PM) and outdoor air pollution in China in relation to asthma, wheeze, rhinitis and eczema among pre-school children: Synergistic effects between antibiotics use and PM10 and second-hand smoke.	Norbäck D, et al. *Environ Internat* 125 (2019): 252–260.
Microbiota and organophosphates.	Roman P et al. N*euroToxicol* 75 (2019): 200–208
Effects of household environmental exposure and ventilation in association with adverse birth outcomes: A prospective cohort study in rural China.	Pan D et al. *Sci Total Environ* 822 (2018): 153519.
Impact of home humidifier on children & eczema.	Wang L et al. *Chinese Sci Bulletin* 61 (2016): 1721–1727.
Household environment, lifestyle behaviors, and dietary habits in relation to childhood atopic eczema in Shanghai, China.	Cai J et al. *Int Arch Occup Environ Health* 90 (2016): 141–159.
Indoor Air Pollution Aggravates Symptoms of Atopic Dermatitis in Children.	Kim AH et al. *Plos One* 10 (2015): e0119501.
Effects of home environment and lifestyles on prevalence of atopic eczema among children in Wuhan area of China.	*Zhang M et al.* Chinese Science Bulletin 58 (2013): 4217–4222.
Symptoms of atopic dermatitis are influenced by outdoor air pollution.	Kim J et al. *J Allergy Clin Immunol* 132 (2013): 495–498.
Exposure to gene-environment interactions before 1 year of age may favor the development of atopic dermatitis.	Lee J-Y et al. Int Arch Allergy Immunol. 2012;157:363–371.
Surveillance of home environment in children with atopic dermatitis: a questionnaire survey.	Lee JH et al. *Asia Pac Allergy.* 2012;2:59–66.
Association between indoor renovation activities and eczema in early childhood.	Herbarth O et al. *Int J Hygiene Environ Health* 209 (2006): *241–247.*
Association between ventilation rates in 390 Swedish homes and allergic symptoms in children.	Bornehag CG et al. *Indoor Air.* 2005;15:275–280.

Overall, monitoring pollutant levels, avoiding known irritants when possible, and adopting gentle skincare practices are practical strategies to mitigate environmental factors that influence the risk and severity of AD.[5]

Statement 3: *Some composite wood materials, flexible plastics, and new paint have all been associated with increased skin barrier damage and vulnerability to AD, representing a new class of underrecognized indoor risk factors for AD.*

Indoor exposure to housing materials commonly used during home renovation is an underrecognized but potentially modifiable risk factor for AD (Table 3). Composite wood products, flexible plastics, adhesives, and freshly applied paint are major sources of volatile organic compounds (VOCs), which can aggravate AD.[15] Indoor VOCs are especially high in newly built houses due to multiple new materials emitting VOC particles.[15]

In a study of over 20,000 mother and newborn pairs, renovation/painting in the house during pregnancy was significantly associated with early infantile AD.[15] Similarly, a study involving over 2,500 children identified a correlation between indoor renovation activities (painting, furniture installation, floor covering), and the development of AD from the antenatal period through infancy and early childhood.[16]

These exposures are particularly relevant during the "nesting process" when families undertake renovations to prepare for a newborn. Advisors speculated that exposure to these risk factors, especially when amplified by limited ventilation (ie, closed doors and windows), can increase the risk of AD in vulnerable individuals. This interpretation is supported by the literature, as moving into a newly built house before 1 year of age has been independently associated with a risk for AD, and indoor renovations within the previous five years have been associated with a higher severity of AD.[17,18]

To mitigate these risk factors, individuals should prioritize proper ventilation and reducing exposure. When possible, low-VOC or VOC-free materials (eg, silica-based wallpaper and plant-based flooring material) should be used in living and sleeping areas.[15] Regular ventilation, via exhaust fans or air filtration systems, may further reduce exposure. For infants and children with AD or increased susceptibility of AD, limiting time spent in freshly renovated rooms and maintaining optimal skin barrier care during periods of increased exposure may help mitigate AD symptoms.

Statement 4: *Evidence supports starting skincare early in life, as ongoing daily use of non-alkaline cleansers and moisturizers can promote a healthy skin barrier and reduce AD flares.*

International guidelines recommend daily moisturization as an integral part of AD management to treat skin barrier dysfunction and hydrate the skin.[2,19,20] Daily moisturizer use from birth to enhance skin barrier function may significantly delay the onset of AD in high-risk infants, and may delay or prevent AD flares when used continuously.[11–13]

Although a systematic review and meta-analysis by Zhong et al found no significant reduction in AD development in infants given prophylactic emollients during the first 6 weeks of infancy (RR 0.84, 95% CI, 0.64, 1.10) compared with the control group, prophylactic moisturizers improved skin condition (RR 0.75, 95% CI 0.62–1.11) in infants at high-risk for AD development (n=8 studies). Overall, the prophylactic application of emollients initiated in early infancy may delay AD, especially in high-risk populations and when used continuously.[11]

Nevertheless, conclusive evidence for the prophylactic use of moisturizers to prevent AD is lacking, and results across prevention trials vary.[21] For example, a large-scale RCT found no evidence that daily emollient use during the first year of life prevents AD in high-risk children.[21] While further research is needed, early and consistent skincare is a low-risk strategy that may benefit barrier function.

Skincare can be introduced within the first weeks of life, using non-alkaline cleansers and applying moisturizer immediately after bathing.[2] Healthcare providers can maximize compliance and outcomes by educating patients on the benefits of liberally applying the moisturizer twice daily to support the skin barrier and to help reduce the incidence of flares.[20]

Statement 5: *Cleansers used in children with AD should be free of potential irritants such as fragrance, alcohol, essential oils, botanicals, and harsh detergents.*

US guidelines recommend limited use of nonsoap cleansers that are neutral to low pH, hypoallergenic, and fragrance-free.[2] While normal skin pH ranges from 4 to 5.5, most soaps are alkaline, leading to skin damage, irritation, and dry skin. Therefore, nonsoap-based surfactants and synthetic detergents (syndets) that are gentle, non-alkaline, and free of potential irritants (eg, fragrance, alcohol, essential oils, botanicals, and harsh detergents) are recommended for better tolerance in children with AD.[2]

Statement 6: *Moisturizers containing skin lipids such as ceramides may offer additional benefits to children with AD by helping to maintain the skin barrier and reducing AD flare-ups.*

Moisturizers are a cornerstone of AD therapy. They increase skin hydration and can lessen AD symptoms, including pruritus, erythema, fissuring, and lichenification.[2] Moisturizers can reduce AD inflammation and severity, as well as lower the amount of prescription anti-inflammatory treatments required for disease control.[2]

However, not all moisturizers are equally effective; both the active ingredients and the vehicle influence clinical outcomes. While head-to-head studies are limited, the ongoing, daily use of moisturizers containing lipids, such as ceramides, has been shown to reduce the rate of AD flares and the need for topical steroid treatment.[22,23]

In a randomized controlled trial (RCT) of infants (n=100) at high risk for AD development based on family history, the intervention group received once-daily full-body application of an emollient containing ceramides and amino acids, while the control arm used an emollient of their choice for dry skin, applied irregularly.[23] In the intervention and control groups, AD was diagnosed in 13.2% vs 25.0% at month 12 (P=0.204) and 19.4% vs 31.0% at year 2 (P=0.296), respectively. Although the observed trend was in favor of the intervention, results were not statistically significant, likely due to lack of power from under-enrolment. Nevertheless, the observed trends suggest a protective effect of the ceramide-containing study emollient therapy compared to control.[23]

US guidelines recommend including moisturizers in AD management plans.[2] For children with AD, recommended moisturizers should be gentle, non-alkaline, free of additives, fragrances, perfumes, and other potentially sensitizing agents, and formulated with barrier-supporting lipids such as ceramides, to support the skin barrier.[2,12]

DISCUSSION

Environmental factors play a key role in the development and severity of AD in children. Potentially and partly modifiable environmental factors that can damage the skin barrier and exacerbate AD flares include climate, air pollutants, allergic sensitization, hard water, and poor skincare. Indoor environmental exposures to composite wood materials, flexible plastics, and new paint have also been associated with increased skin barrier damage and vulnerability to AD. Many of these exposures are potentially modifiable, presenting opportunities for risk mitigation, particularly early in life when the skin barrier is still developing.

Evidence supports early initiation of skincare, with some studies reporting benefits of consistent daily use of non-alkaline cleansers and moisturizers to promote a healthy skin barrier. Applied from birth onwards, gentle cleansers and moisturizers

containing barrier lipids may help maintain the protective skin barrier, possibly delaying AD occurrence and severity in predisposed infants.

Limitations

AD is a complex disease influenced by genetic, microbial, and environmental factors. This manuscript focuses on environmental contributors to AD and is not intended to provide a comprehensive review of all pathogenic mechanisms. The literature review was limited to studies published between 2010 and 20th January 2025 and therefore does not capture research published beyond this period. The systematic search was also restricted to English-language publications; relevant evidence published in other languages was not included.

CONCLUSION

The current understanding of AD has broadened to include the complex interplay between SAIGE factors. While the environment has long been recognized as a contributor to AD, it now represents a heightened risk due to increasing urbanization and climate change. Clinicians have an opportunity to mitigate the impact of these environmental factors in vulnerable neonates and young children by using appropriate cleansers and moisturizers. While more evidence is needed, early and consistent use of non-irritating, barrier-supportive skincare may help promote a healthy skin barrier and reduce AD flares in high-risk children.

DISCLOSURES

This work was supported by an educational grant from CeraVe US. The authors (LAS, AA, LB, MEG, PK, PL, RS, VA, NBS) received fees for attending the meeting. All authors (LAS, AA, LB, MEG, PK, PL, RS, VA, NBS) contributed to the development of the manuscript, reviewed it, and agreed with the content and publication.

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doi:10.36849/JDD.9507R2

October 2026 943 Volume 25 • Issue 10

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

A Narrative Review of Seven Off-Label Treatment Options for Seborrheic Dermatitis

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ABSTRACT

Background: Seborrheic dermatitis (SD) is a chronic inflammatory skin condition driven by overactive sebaceous glands, Malassezia colonization, immune dysfunction, and epidermal barrier disruption. While topical corticosteroids and antifungals are first-line treatments, rebound disease and adverse effects limit long-term use.

Objective: To evaluate 7 off-label therapies for SD: topical calcineurin inhibitors (TCI), metronidazole, phosphodiesterase-4 inhibitors (PDE4), systemic antifungals, isotretinoin, natural remedies, and microbiome-directed therapies.

Methods: A PubMed-based narrative review included clinical trials, observational studies, and case reports when higher-level data were lacking.

Results: TCIs and PDE4 inhibitors demonstrated consistent efficacy for facial SD as steroid-sparing options. Metronidazole provided modest benefit, mainly in patients with concomitant rosacea. Both systemic antifungals and low-dose isotretinoin were effective for moderate-to-severe disease, though systemic therapy requires monitoring for hepatotoxicity. Natural agents (eg, honey, tea tree oil) and microbiome-targeted therapies (eg, probiotics, Triphala) showed variable improvement.

Conclusion: These therapies serve as promising treatment options for SD, particularly in refractory cases or when standard treatments are unsuitable. Larger comparative trials with standardized outcomes and long-term follow-up are needed to clarify their role.

J Drugs Dermatol. 2026;25(10):943-948. doi:10.36849/JDD.9507R2

INTRODUCTION

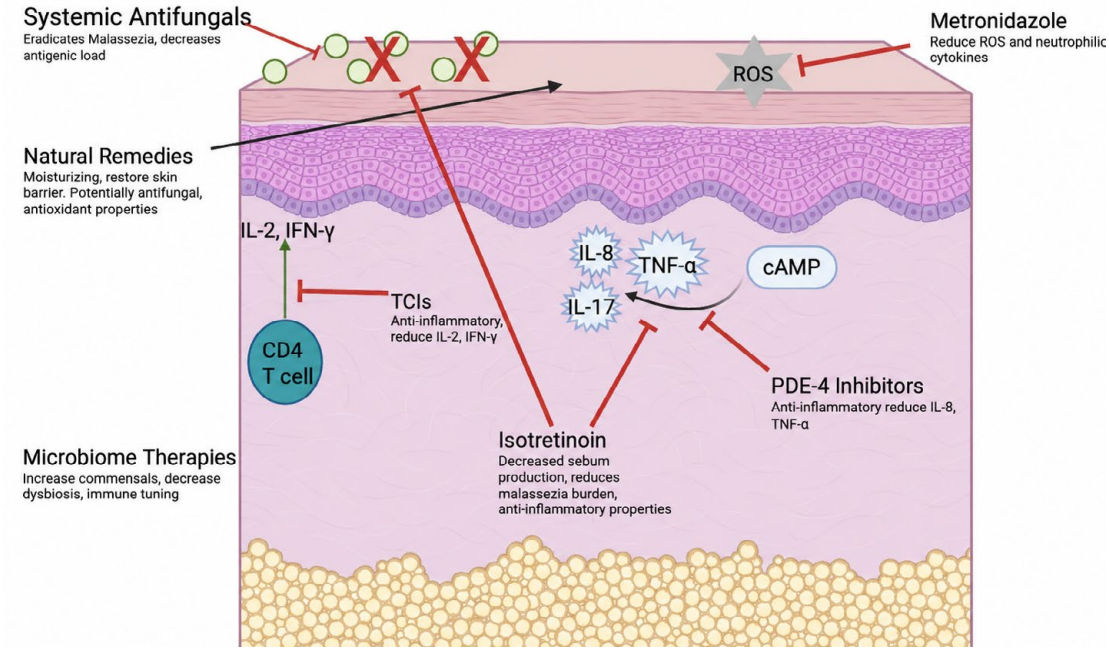
Seborrheic dermatitis (SD) is a chronic, relapsing inflammatory condition that predominantly affects sebaceous gland-rich areas such as the scalp, face, and chest.[1] Characterized by erythematous scaly patches, SD affects up to 5% of the general population and has a higher prevalence in individuals with immunosuppression or neurologic disease.[2] SD arises from multifactorial interactions among sebaceous activity, Malassezia colonization, immune dysregulation, and barrier dysfunction.[3] First-line therapies (topical corticosteroids and topical antifungals) often achieve short-term control but are limited by frequent relapse and adverse effects such as atrophy and telangiectasia.[4] These challenges highlight the need for safe, durable alternatives. Emerging evidence supports several adjunctive and off-label options targeting immune modulation, inflammation, microbial balance, and barrier repair (Figure 1). This narrative review synthesizes data across seven such treatments, including topical calcineurin inhibitors (TCIs), metronidazole, phosphodiesterase-4 (PDE4) inhibitors, systemic antifungals, isotretinoin, natural treatments, and microbiome-modulating therapies. Due to length limitations, the full table underlying the summarized results is not included in the manuscript. The complete dataset is available at: https://doi.org/10.6084/m9.figshare.30815681 or from the corresponding author upon request.

Topical Calcineurin Inhibitors

Ten studies (n=367; 9 facial, 1 scalp) evaluated pimecrolimus 1% cream and tacrolimus 0.1% ointment applied twice daily for SD.[5-14] Pimecrolimus demonstrated rapid and significant improvement in erythema, scaling, and pruritus, with >80% reduction in composite severity scores reported in multiple studies.[5,7,9]

Tatlican et al observed a mean cure time of 13.3 days and remission duration of 48 days, while Kim et al reported >85% of patients rated "almost clear" or "clear" after 4 weeks.[5,7]

FIGURE 1. Mechanistic pathways targeted by adjunctive therapies in seborrheic dermatitis. This diagram illustrates the key pathophysiologic processes involved in seborrheic dermatitis and highlights the therapeutic targets of various adjunctive and off-label treatments. Systemic and topical antifungals reduce Malassezia colonization and associated antigenic load. Topical calcineurin inhibitors (TCIs) inhibit T-cell activation, reducing IL-2 and IFN-γ–driven inflammation. Phosphodiesterase-4 (PDE4) inhibitors downregulate cAMP-mediated expression of IL-8 and TNF-α. Metronidazole attenuates oxidative stress and neutrophil-associated cytokine production. Natural remedies may exert mild antifungal, anti-inflammatory, and barrier-restorative effects. Microbiome-targeted therapies aim to restore commensal balance and modulate cutaneous immune signaling.



Tacrolimus showed comparable outcomes. Meshkinpour et al noted complete clearance in 61% of 18 patients with mean severity reduction from 27% to 7%.[8] In a split-face trial, tacrolimus demonstrated equivalent efficacy to ketoconazole with higher patient satisfaction and greater pruritus relief.[10] Shin et al found faster improvement and longer remission than zinc pyrithione or betamethasone.[6]

Adverse events were mild and transient, occurring in 16% to 45% of pimecrolimus-treated and fewer tacrolimus-treated patients, most commonly burning or tingling.[5-8] No serious adverse events were reported. Comparative trials showed pimecrolimus was non-inferior to hydrocortisone, and similar in efficacy to sertaconazole, with patient satisfaction rates between 80 and 90%.[11-13] Collectively, TCIs demonstrate strong evidence from randomized controlled trials (Level I) and open-label studies (Level III), establishing them as effective, well-tolerated, steroid-sparing options for facial SD.

PDE-4 Inhibitors

Six studies (total n=176) assessed topical or oral PDE4 inhibitors for SD, primarily roflumilast formulations.[15-20] In a phase 3 trial of 154 patients, 73.3% of patients achieved an Investigator Global Assessment (IGA) score of clear or almost clear, compared with 40.3% in the vehicle group (P<0.001).[16] Smaller studies reported clearance or marked improvement within 1 and 8 weeks.[15,17,20] Liu et al described symptomatic relief using crisaborole 2% ointment, and Cohen et al reported complete or near-complete response in 3 patients receiving oral apremilast 30 mg twice daily.[19] Adverse effects were minimal; mild localized irritation occurred in 2.6% of roflumilast-treated patients, with no serious events reported.[16]

Metronidazole

Seven studies (total n=519) evaluated topical metronidazole (0.75% or 1% gel) for SD.[21-27] Three randomized trials reported statistically significant improvement vs placebo. Parsad et al reported marked or complete clearance in 14 of 21 patients by week 2 compared with 2 of 17 receiving placebo (P<0.001).[22] Siadat et al found good-to-excellent response in 50% vs 22.2% with placebo (P<0.001), and Seckin et al observed clinical improvement in 81.5% vs 44.4% (P<0.05).[23,24] Two larger trials (Ozcan et al, Koca et al) found no significant difference from placebo in 67 and 84 patients, respectively, with frequent relapse after discontinuation.[21,27] Comparative studies reported lower patient satisfaction for metronidazole (56%) than sertaconazole (87%) and lower efficacy than pimecrolimus, with 70% relapse by day 21.[25,26] Adverse events were uncommon and mild, limited

to transient erythema or xerosis, with no serious reactions.[22,23] Evidence strength is moderate-to-low (Level II–III), showing variable clinical benefit.

Systemic Antifungals

Seven studies (total n=365) assessed systemic antifungals for moderate-to-severe or refractory SD cases.[28-36] Itraconazole 200 mg/day, in short or pulse regimens, produced significant improvement in disease severity in multiple trials, with sustained benefit with monthly maintenance dosing.[28.30,31] Baysel et al and Thu Do et al reported reduced relapse rates and durable remission with maintenance therapy.[32,34] Fluconazole 300 mg weekly showed limited efficacy.[29] Adverse effects were uncommon and mild, including transient gastrointestinal discomfort and asymptomatic elevations in liver enzymes; no serious events were recorded.[28-34] Systemic antifungals demonstrate consistent efficacy and acceptable safety for refractory or widespread SD, though dosing schedules and duration require further standardization and patient monitoring for hepatotoxicity.

Isotretinoin

Multiple studies have evaluated oral isotretinoin for moderate-to-severe SD, particularly with facial and truncal involvement.[37,38] In a retrospective cohort of 234 patients, Demirbas et al compared 10 mg or 20 mg daily dosing, finding greater reductions in Seborrheic Dermatitis Area and Severity Index (SDASI) and Dermatology Life Quality Index (DLQI) with 20 mg at 12 months (P<0.001). Higher dosing also reduced recurrence risk (OR = 0.131, 95% CI 0.037–0.459, P=0.002) and improved satisfaction and long-term remission rates.

A 2023 systematic review of 7 studies (n=229) reported a pooled mean dose of 9.2 mg/day for 4 months, with 96% of patients achieving partial and 45% complete or excellent clearance.[38] Pruritus improved by a mean of 81.9% (95% CI: 68.5–95.2%, P=0.003 vs itraconazole), and relapse remained low (11.1%) 3 months post-treatment. Collectively, isotretinoin shows substantial efficacy and durable control with low relapse rates in moderate-to-severe SD.

Natural Remedies & Botanicals

Five studies (total n=398) evaluated natural and botanical agents for SD.[39-43] In a 30 patient trial, Al-Waili et al reported significant improvement in itching, scaling, and lesion healing using 90% crude honey in warm water every other day for 4 weeks, with no relapse in the prophylaxis group vs 80% in controls.[39] Igielska-Kalwat et al observed resolution of symptoms and reduced sebum in 50 patients using a Pyretrin-D trichological regimen for 100 days.[40] Satchell et al found 41% severity improvement with 5% tea tree oil shampoo compared with 11% for placebo (P<0.001).[42] Gupta et al noted frequent use of coconut and mustard oil among 150 pediatric patients, though no formal efficacy scores were recorded.[41] No serious adverse events were reported; tolerability was excellent.[39-43] Evidence quality remains limited (Levels I, III), indicating modest benefit and high safety in mild or adjunctive SD management.

Microbiome-Targeted Therapies

Four studies (total n=231) evaluated microbiome-targeted therapies for SD.[43-46] Truglio et al reported significant reductions in SDASI scores among 35 patients using a probiotic-rich topical suspension (Eutoplac) twice daily for 4 weeks, with decreased Malassezia density and increased bacterial diversity.[44] Fithian et al observed significant improvements in IGA, Total Severity Score (TSS), and parent-reported symptoms (P<0.001) in 42 pediatric patients using a topical probiotic formulation containing honey, turmeric, and vitamin B12 for 2 weeks.[43] Guéniche et al demonstrated a 62.7% reduction in clinical score and 73.4% pruritus with 5% Vitreoscilla filiformis biomass lotion daily for 4 weeks vs 26.1% and 49.4% with vehicle (P<0.0001, P=0.01).[46] Microbiome-targeted therapies offered moderate efficacy and favorable tolerability (Level II, III), supporting their role as adjuncts for restoring microbial balance in SD.

DISCUSSION

SD remains challenging due to its chronic-relapsing nature and the limitations of standard therapies such as topical corticosteroids and antifungals. Although these agents are moderately effective for acute control, symptoms often recur shortly after discontinuation, contributing to cosmetic distress and reduced quality of life, particularly in facial SD.[45,46] Long-term corticosteroid use is further constrained by adverse effects including atrophy and telangiectasia.[4] These limitations have prompted investigation into alternative or adjunctive options aimed at improving tolerability, durability of remission, and patient adherence. This review synthesized evidence across seven therapeutic domains (TCIs, PDE-4 inhibitors, metronidazole, systemic antifungals, isotretinoin, natural agents, and microbiome-directed therapies) to characterize their efficacy and safety profiles (Figures 2 and 3).

Pimecrolimus and tacrolimus demonstrated consistent efficacy across multiple randomized and open-label studies (Levels I and III evidence).[5-13] Most trials reported rapid reduction in symptomology, with some as high as 85% rates of almost clear or clear in 2 to 4 weeks.[5] TCIs were non-inferior to hydrocortisone and as effective as topical ketoconazole, confirming their utility as steroid-sparing alternatives for cosmetically sensitive areas. Although remission can last several weeks after cessation, relapse remains common, warranting further study of maintenance regimens.

PDE4 inhibition offers a mechanistic approach that reduces pro-inflammatory cytokine activity through cAMP modulation. Clinical studies demonstrated moderate efficacy, with

FIGURE 2. Evidence grid for adjunctive and off-label therapies in seborrheic dermatitis. This heat map summarizes comparative performance across 4 therapeutic dimensions, efficacy, safety, evidence strength, and relapse prevention, for selected adjunctive and off-label treatments in seborrheic dermatitis. Each domain is scored on a 1–5 scale based on available clinical trial data, mechanistic rationale, and long-term treatment outcomes. A score of 5 reflects the most favorable outcome (eg, high efficacy or strong evidence base), while 1 represents limited or unfavorable data, providing a visual overview of therapeutic strengths and limitations to guide clinical decision-making and future research prioritization.

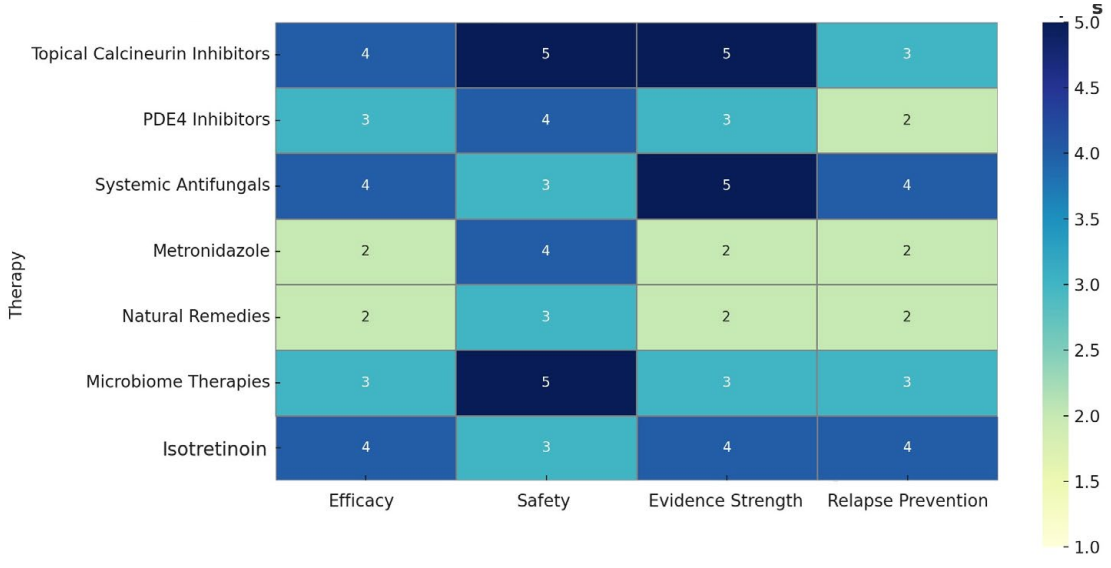


FIGURE 3. Summary matrix of adjunctive and off-label therapies for seborrheic dermatitis. This table summarizes therapeutic options evaluated in this review, categorized by drug class. Each entry includes the number of supporting studies, a representative "best-evidence" intervention, and a qualitative rating of evidence strength based on available clinical data. Background color corresponds to the strength of evidence: green (strong), orange (moderate), and red (limited). Notes highlight key clinical considerations such as efficacy, safety, or positioning within the treatment algorithm.

Therapy Class	# of Studies	Best-Evidence Study	Evidence Strength	Notes
Metronidazole	7	Metronidazole 0.75% gel applied BID	Limited	Useful for rosacea overlap, limited trials
Microbiome-Targeted Therapies	2	Topical suspension containing EUTOPLAC	Moderate	Novel mechanism, early-phase studies
Natural Remedies	5	Crude honey 90% in warm water	Limited	Heterogeneous formulations
PDE4 Inhibitors	6	Roflumilast 0.3% cream, once daily	Moderate	Oral formulation lacks RCTs
Systemic Antifungals	6	Itraconazole, 200 mg/day, pulse therapy	Strong	Effective for scalp/widespread SD
Topical Calcineurin Inhibitors	11	Pimecrolimus cream 1%, twice daily	Strong	Steroid-sparing, well studied
Sertaconazole	3	Sertaconazole 2% cream vs Hydrocortisone 1%	Strong	Dual antifungal + anti-inflammatory; effective and well-tolerated for facial SD
Isotretinoin	2	Isotretinoin 10–20 mg daily, oral	Moderate	Effective for facial SD; dose-dependent relapse prevention and high satisfaction

roflumilast 0.3% foam now FDA-approved for patients >9 years old. A recent phase 3 clinical trial found evidence for rapid symptom relief and high clearance rates, with 73.3% achieving a score of clear or almost clear with favorable safety profiles.[16] Their ability to produce rapid results (as early as 1 week) in reduction of symptoms while being non-steroidal makes them a particularly attractive option.[20] Oral PDE4 inhibitors remain underexplored, with only a single case series published to date that reported near-complete clearance in three patients treated with apremilast.[19] Larger head-to-head trials comparing topical PDE4 inhibitors with TCIs and systemic antifungals are needed to define relative efficacy and durability.

Evidence for metronidazole is inconsistent. Level II–III data support modest benefit in mild-to-moderate cases, particularly among patients with concurrent rosacea.[22] While several trials report excellent response rates, others found no difference vs placebo.[21,24,27] Relapse within 3 weeks of discontinuation was common, and comparative studies demonstrate inferior outcomes relative to sertaconazole and pimecrolimus.[25,26] Metronidazole's excellent tolerability and lack of steroid-related side effects make it an option for steroid-intolerant patients; however, its limited and transient efficacy restricts broader application. Standardized outcome measures and evaluation in combination regimens may help clarify its role.

Systemic antifungals, particularly itraconazole, are highly effective in moderate-to-severe or refractory SD, especially with scalp involvement and widespread disease if topical treatments have proven ineffective. The dual-pronged approach of Malassezia reduction and anti-inflammatory properties yields a durable response, especially with pulse or maintenance dosing regimens.[28,30,31,32,34] From a side effect standpoint, they were well-tolerated, with 3 patients reporting mild GI upset. Hepatotoxicity risk and medication interactions warrant monitoring, yet the overall risk-benefit profile supports use in refractory, widespread, or scalp-predominant SD when topical therapy is inadequate.[28-36] Standardized dosing protocols and longer-term data remain areas for further research.

Isotretinoin reduces sebaceous gland size and sebum production, limiting Malassezia proliferation and inflammatory activation.[37,38] Across cohort and pooled analyses, low-dose regimens (10–20 mg/day) significantly decreased SDASI and DLQI scores, improved quality of life, and reduced recurrence rates compared with antifungal therapy. These findings support isotretinoin as an effective systemic option for moderate-to-severe or refractory SD. Future randomized studies should determine optimal dosing duration and better define its role in maintenance therapy.

Natural remedies such as honey-based formulations, tea tree oil, and polyphenol-rich preparations demonstrate modest but reproducible improvements in symptoms, with excellent safety.[39-43] Studies on honey and tea tree oil reported significant symptom improvement (eg, 41% severity score reduction with tea tree oil).[39] These options might be particularly useful in patients with mild SD, patients seeking non-pharmacologic options, or pediatric and steroid-averse populations. Although these agents may serve as adjuncts or alternatives for mild disease and steroid-averse or pediatric patients, evidence is limited by small sample sizes and heterogeneous protocols. Standardization of formulations and controlled trials are necessary to better characterize efficacy.

Beyond Malassezia spp., emerging research implicates bacterial dysbiosis, including disruptions in Cutibacterium and Lactobacillus, in SD pathogenesis. Microbiome-directed therapies, including probiotics, prebiotics, and bacterial lysates, represent a conceptual shift in SD treatment and are supported by Level II–III evidence demonstrating moderate efficacy. These therapies aim to rebalance the skin microbiome by enhancing bacterial diversity and have yielded reductions in SDASI, clinical scores, and pruritus by up to 73.4%.[44] Furthermore, they maintain an excellent safety profile with minimal adverse events. These therapies may offer novel maintenance strategies or relapse prevention tools; however, the evidence is preliminary, and larger, comparative trials are needed to establish their efficacy relative to standard treatments and to optimize delivery methods.

Despite encouraging findings, the current literature suffers from limitations: small sample sizes, short study durations, lack of standard outcome measures, and limited head-to-head comparisons. Cost, accessibility, and long-term safety are infrequently addressed, diminishing real-world applicability. Additionally, many promising studies are published in lower-impact journals, reducing their visibility despite clinical relevance. Ultimately, while traditional therapies remain essential, the evolving landscape of off-label and adjunctive options provides clinicians with an expanded, patient-centered toolkit. Thoughtful integration of these strategies, guided by evidence, patient preferences, and long-term safety considerations, may enhance treatment durability and improve quality of life for patients with chronic SD.

CONCLUSION

SD remains a challenging condition to manage long-term, particularly in patients who are steroid-intolerant, relapse-prone, or seeking more holistic care. The expanding range of off-label and adjunctive treatments, including immunomodulators, anti-inflammatories, natural remedies, and microbiome-targeted interventions, offers new opportunities for individualized, mechanism-based therapy. While current evidence is promising, larger, high-quality trials are essential to validate these approaches, optimize treatment algorithms, and ultimately improve outcomes for patients living with this burdensome disease.

DISCLOSURES

Dr Jay Wolverton was previously an investigator for Galderma. He also previously served on an advisory board for Johnson & Johnson. The other authors have no conflicts of interest to declare.

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doi:10.36849/JDD.9660

October 2026 949 Volume 25 • Issue 10

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Nordic European Countries Atopic Dermatitis (NECAD) I: Importance of Concordance With Skincare for Atopic Dermatitis

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ABSTRACT

Background: Atopic dermatitis (AD) is a chronic disease with a dysfunctional skin barrier, requiring continuous management to reduce symptoms and prevent flares. Topical treatment comprises the cornerstone of AD management. The paper's objective was to summarize current recommendations for skincare in AD, addressing challenges and possible interventions for improved concordance. Method: The *Nordic European Countries Atopic Dermatitis* (NECAD) panel of dermatologists discussed surveys, literature, and professional experiences regarding skincare in AD management. Five consensus statements were established to share general insights and suggestions to improve treatment concordance.

Results: Skincare with emollients is the recommended basis of AD management. Concordance to topical treatment is considered a significant challenge in AD. Evidence suggests that newer, more comprehensive emollients are superior to basic emollients regarding both clinical effect and convenience in patients' daily routine. Interventional tools such as evidence-based patient education, AD action plans, and closer physical and/or digital follow-up were suggested.

Conclusion: The effectiveness of topical treatment in AD is highly dependent on the type of emollient used as well as patient concordance. With increasing evidence and focus on patient education, concordance and, thus, treatment outcomes can be improved.

J Drugs Dermatol. 2026;25(10):949-955. doi:10.36849/JDD.9660

INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing skin disease presenting with inflammation, pruritus, and xerosis.[1,2] A family history of atopy and related comorbidities such as asthma and allergic rhinitis is often seen in AD patients, particularly associated with severity and early onset.[3] Generally, AD is the most common skin disease in young children, and exacerbations are common and may present lifelong.[1,2] Flares are associated with sleep deprivation, stigmatization, social withdrawal, anxiety, and depression, and may substantially impact quality of life.[4]

The main clinical characteristics of AD typically include erythema, edema, excoriations, and xerosis.[1] However, characteristics differ depending on age and ethnicity, which trained dermatologists can identify and distinguish, but may be challenging for other healthcare providers such as general practitioners (GPs).[2,5]

AD is pathologically characterized by its skin barrier dysfunction, which commonly, but not exclusively, is driven by specific filaggrin gene mutations and downregulation of filaggrin and other skin barrier proteins due to inflammation.[2,6] Xerosis is a prominent feature that leads to irritation, micro-fissures, and cracks, due to decreased amount of skin lipids in AD-affected skin and increased transepidermal water loss (TEWL). Additionally, the skin barrier dysfunction leaves the skin more susceptible to bacterial colonization, particularly *Staphylococcus aureus*, contributing to exacerbation and a higher skin infection rate.[1,7]

External factors, ranging from climate to skin products, can significantly impact AD, either positively or negatively. In comparison to sunny, humid climates, the cold and drier Nordic climates increase the burden of AD. Skin products containing irritants and allergens can negatively affect the skin barrier, whereas specialized moisturizing products support better skin barrier function. Early microbiome alteration has also been suggested as a possible mechanism for decreasing both AD severity and risk of developing atopic comorbidities.[3]

Globally, AD presents with a high burden of disease for both patients and caregivers, including dermatological, pediatric, and general practice, but also families of young AD patients.[5,8]

According to international guidelines, daily use of moisturizing skincare, with so-called emollients, is considered the basis of AD management, as it may prevent flares and reduce symptoms.[9] Specifically, emollients with hydrophilic formula in summer and higher lipid content in winter, and gentle cleansing/bathing with no irritants, are the gold standard recommendation.[10] Some studies suggest that following recommendations from the earliest possible time point may be determinant for AD-prone infants' patient journey, reducing frequency and severity of flares and intervening with the atopic march development of asthma, allergic rhinitis, or food allergies.[11,12] Increasingly, studies indicate that emollients are not created equally and that selecting the right emollient for the individual patient is crucial. Regrettably, non-concordance to topical treatment has proven a significant challenge in AD.[13-15] Patients' reasons for not using prescribed emollients range broadly from a sticky or stinging feeling to failing establishment of a daily routine or not experiencing a swift, positive effect. Treatment adherence is crucial for optimal effect, and non-concordance is a major limiting factor for positive treatment outcomes in AD.[13,15] Although AD topical treatment adherence is understudied and proven difficult to assess and compare, studies have shown 40% adherence to as short as 5-day treatment regimens, and down to 30% adherence to 8-week treatment plans.[13-15,16] New approaches to improve concordance may improve the AD patient journey, particularly for better distinction between non-concordance and non-response in individual patients.[14]

The objective of this paper was to establish and discuss 5 consensus statements addressing the importance of, and related challenges with, concordance to emollient use in AD patients, and suggesting potential interventions for improvement.

MATERIALS AND METHODS

NECAD Panel Meeting

A panel of advisors, consisting of five dermatologists from Nordic European countries and one from the UK, who treat AD patients, participated in a consensus meeting on March 8, 2025. The panel aimed to describe and discuss the importance of concordance with skincare, including wash products and emollients, in AD management. The advisors identified risk factors associated with non-concordance with basic skincare and explored the significance of the right skincare, particularly emollients, for individual AD patients. Available Nordic market surveys were added as discussion points for the advisors.[17-19] Working in small groups, the advisors revised draft statements based on the literature, surveys, and their own professional opinions and clinical experience. They then reconvened as a plenary group to reach consensus on 5 statements through blinded reiterations. Subsequent reviewing and editing of the manuscript took place online.

Definition of Concordance

Current medical practice encompasses a holistic approach to patient care, integrating a disease's social, psychological, and pathological aspects. Treatment adherence is essential for improving treatment outcomes. The concept of concordance respects the patient's integrity, autonomy, and self-determination, encouraging the patient to actively and equally participate in their comprehensive treatment regimen. This approach establishes a collective therapeutic alliance, based on trust and communication, fulfilling both patient and physician aspirations and expectations.[20]

Literature Review

Prior to the meeting, the literature on concordance and current best practices on skincare in AD management was compiled. On January 8, 2025, exploratory searches were performed on PubMed and Google Scholar by reviewing titles and abstracts, then full articles, using the search terms: atopic dermatitis AND skincare OR cleansers OR emollients OR adherence OR compliance OR concordance to treatment. Selected articles included clinical guidelines, algorithms, consensus papers, systematic literature reviews, and clinical studies published in English between January 2015 and 2025. Publications in non-English or not addressing adherence/compliance/concordance with skincare for AD were excluded. Two reviewers (AA/HA) independently evaluated the search results, manually reviewing the selected publications. Database searches identified 63 records, of which 25 articles were included; see Figure 1 for the flowchart.

RESULTS AND DISCUSSION

Nordic Survey Insights

Surveys on the Nordics' emollient use in AD patients provided insights into the market and the experiences and options of prescribers and patients in the different Nordic countries (Table 1).[17-19]

Consensus Statements

Statement 1: *Topical medications are the mainstay of treatment, and when used as directed, they are highly effective; but poor concordance yields poor treatment outcomes and high costs.*

FIGURE 1. Flowchart of literature search.

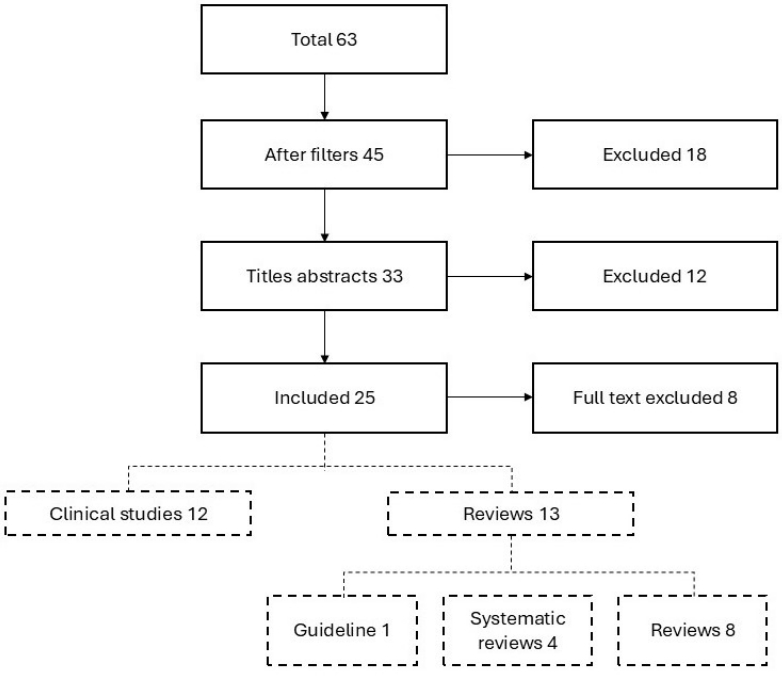


TABLE 1.

Survey Insights Into Nordic Countries Market, Prescribers and Patients		
Market Insights	**Prescriber Insights**	**Patient Insights**
Norway / Sweden: • Skincare prescription *or* recommendation. Reimbursement depends on emollient being registered as drug (OTC). Finland: • Skincare prescription *or* recommendation. Reimbursement depends on emollient being produced under Pharma GMP. Denmark: • Skincare recommendation only. No general emollient reimbursement.	All Nordic countries: • Skincare with emollients is a cornerstone in AD treatment • Patient education in emollient use, regardless of AD severity, is crucial • Individualized medical recommendations may improve compliance, but research evidence is scarce • Concordance challenges include vast market of products, high costs for patients and patient dissatisfaction of formulations	All Nordic countries: • 90% of patients report picking up prescribed emollient • ~40% of patients do not use the emollient as recommended • Poor compliance is due to one or several of the following objections: 43% greasy/sticky feeling 15% stinging upon application 23% not experiencing improvement 20% not establishing a daily routine

Abbreviations: OTC, over-the-counter (non-prescription) drug; GMP, good manufacturing practice; AD, atopic dermatitis.

Topical treatment of AD consists of a ground basis of emollients for improving skin barrier function and topical medications, mainly addressing the inflammatory component of AD. Additionally, dysbiosis in AD may require topical antibiotics, but the risk of resistance development limits their use. In combination, topical treatment is generally highly effective when used as recommended.[9] However, non-response to topical treatment is common in AD, which is mainly believed to be due to poor concordance.[14] Early intervention appears important in AD-prone infants to reduce the number and severity of flares, as well as decrease their risk for development of AD comorbidities, including asthma, food allergies, and allergic rhinitis (Table 2).[3-11]

Statement 2: *Poor concordance may be related to multiple factors comprising forgetfulness, time-consuming topical treatment, financial burden, lack of a trusting physician-patient relationship, dislike of the prescribed/recommended vehicle, poor understanding of the disease and proper application of medication or skincare.*

TABLE 2.

Topical Treatments for Atopic Dermatitis	
Severity of AD	**Topical Treatment**
Severe	High potency TCS + TCI + emollients
Moderate	Medium potency TCS + TCI + emollients
Mild	Low potency TCS + TCI + emollients
Controlled	TCI or TCS + emollients
Maintenance (to areas of predilection)	TCI or TCS + emollients
Long-term maintenance and prevention	Gentle wash products and emollients

Abbreviations: TCS, topical corticosteroid; TCI, topical calcineurin inhibitor.

Since AD is a chronic skin disease, it requires continuous, long-term management, which has proven to be a significant challenge. Poor concordance to daily emollient use is a major factor limiting treatment outcomes in AD patients. Concordance, and the lack thereof, may be related to challenges in the daily routine, significant time-consumption with application, as well as related costs, which can be substantial.[15,20,21]

Low degree of patient knowledge and understanding of AD, and the necessary, continuous effort in topical management, may further reduce concordance. It may also be associated with suboptimal physician-patient relationships or general dislike of or objection to the prescribed products, as seen in steroid phobia.[20,22]

Clinicians should consider patients' lifestyle, convictions, and preferences during the development of individual treatment plans.[9] Shared decision-making is essential, as implementation of daily routines and treatment may involve the whole family, and in some cases, a psychosocial approach or intervention is required.[20,23]

Additionally, helping patients identify products and/or ingredients to avoid can support individualized topical treatment plans. Clinicians should be able to provide information on emollients and wash products in general, to establish a good physician-patient relationship, and to prevent patients from seeking skincare information from non-scientific sources, such as retailers or social media.

Increased treatment concordance could contribute to significant cost reduction for both patients and healthcare systems, reducing the need for avoidable visits and multiple medication changes.

Statement 3: *Interventions, including patient education by an atopic dermatitis educator or nurse consultation, AD written action plans, and a shorter time to the first follow-up visit, appear to improve concordance and treatment outcomes.*

To improve concordance, several potential interventions may be considered and discussed. There is a strong agreement on the importance of patient education, but specific tools need to be identified.[4,13,15] Firstly, setting aside extra time in first consultations, or providing subsequent nurse consultations for both environmental education and treatment explanation, may significantly increase patient knowledge.[7] This can be supplemented by written information and hand-outs such as AD action plans.[24] Therapeutic patient education programs are important for both children and adults with AD.[9,23] Particularly, in the beginning of new treatment regimens, closer follow-up visits may be a beneficial long-term investment, both due to *"white-coat adherence"* and for appropriate, timely treatment adjustment.[25-27] Additionally, adequate supply and refill volumes of prescribed topicals are crucial for maintaining concordance.[23]

Providing product samples may motivate patients to try different products to find a good match, depending on individual preferences. Practical tips for implementation into daily routine include, eg, placing emollients next to the patient's toothbrush. When available, informing patients that products are supported by evidence in the scientific literature can contribute to persuading patients to use emollients. Dermatologists should improve at explaining the scientific background of different emollients. Increased focus on appropriate education in providing adequate patient information on emollient use should be prioritized. This is particularly relevant for dermatologists, GPs, and nurses, given the potential for both limited consultation time and long waiting lists for dermatological consultations. In general, GPs have limited dermatology training and cannot be expected to provide adequate patient information on emollients without additional education.

Statement 4: *Even in the absence of active disease, the chronic nature of AD requires ongoing basic care to maintain the skin barrier and prevent future flares*

Emollients reduce the need for active treatment, preventing AD flares, and restore the skin barrier function.[28] Emollients should be used as part of a daily routine, and choosing the right emollient for the individual patient matters.

TABLE 3.

Key Properties of Emollients		
Property	**Effect**	**Ingredient Examples**
Occlusive barrier	Reduce transepidermal water loss	Liquid paraffin; white soft paraffin; petrolatum
Film formers	Support a protective barrier	Dimethicone
Preservatives	Preserve formulation	Propylene glycol; Phenoxyethanol
Humectants	Bind water molecules	Glycerin/glycerol; Sodium hyaluronate; Urea; Carboxylic acid
Physiologic lipids	Supply components of the stratum corneum lipid matrix	Triglycerides ceramide NP, AP, EOP ; fatty acids; Phytosphingosine; Cholesterol
Emulsifiers	Mix oil- and water-soluble ingredients	Cetomacrogol; Cetostearyl or Cetearyl or Cetyl alcohol; Ceteareth- 20; Sodium lauroyl lactylate; Multivesicular emulsion (MVE)
Vitamins	Induce skin cell turnover and ceramide production or anti-oxidant or anti-inflammatory effects	Vitamin B3 (Nicotinamide); Vitamin E (Tocopherol); Vitamin A; Vitamin C

In healthy skin, a structured lipid matrix of ceramides, cholesterol, and fatty acids creates a strong skin barrier, reducing TEWL.[28] In AD, this structure is disrupted, leading to increased TEWL and allowing easier penetration of irritants and allergens. Use of emollients for AD has several benefits, highly dependent on the emollient type and level.

There are 3 levels of emollients:

1. Level 1: occlusive emollient – a simple formulation that reduces TEWL, reducing dehydration.
2. Level 2: occlusive emollient with humectant – an enhanced formulation that additionally binds water, increasing hydration.
3. Level 3: occlusive emollient with humectant and physiological lipids – a comprehensive formulation that additionally restores the skin barrier.

Other key emollient properties include film formers, emulsifiers, vitamins, and preservatives. See Table 3 for an overview of the key properties of emollients.

Emulsifiers are necessary for mixing lipid- and water-soluble ingredients. An emulsifier alone may have properties that can negatively affect the skin, but additive ingredients like humectants and physiological lipids may neutralize these effects. In more newly developed emollients, *"Multivesicular Emulsion"* (MVE) technology allows for packaging of lipids without emulsifiers, decreasing the concentration of conventional emulsifiers, so that their adverse effect is reduced substantially.[29,30]

Vitamins are widely used as emollient ingredients for a range of different, vitamin-specific properties, including skin cell turnover, anti-inflammatory, or antioxidant effects. Particularly relevant in emollients for AD is nicotinamide (vitamin B3), which contributes to restoring the skin barrier by inducing ceramide production.[31]

Preservatives are necessary in most skincare products, but they may have negative properties. For instance, propylene glycol, a good preservative, can induce stinging. Toxic ingredients, protein allergens, and haptens should be entirely avoided in skincare.

A market-available level 3 emollient based on MVE technology was investigated in 2 studies in direct comparison to level 1[29] and 2[30] emollients, respectively. The trials were double-blinded randomized controlled trials (RCTs) involving twice-daily application for 4 weeks. Overall, the level 3 emollient was shown to deliver essential skin lipids deep within the stratum corneum (SC), enhancing lipid structure.[29,30] It was also superior in increasing SC water content, maintained better skin integrity with lower TEWL, and was more practically and cosmetically acceptable for patients.[29,30]

Early prevention, or delay of AD onset, with daily emollient use on infants has been of particular interest.[32] Trials have investigated daily use during infancy of a level 1 emollient for the prevention of AD.[12,33] The prevalence of AD between the no emollient and the daily level 1 emollient group did not show any difference after 1 year.[33] Instead, the data suggested that the level 1 emollient group presented with an increase in food allergies, which was considered an indication that the skin barrier was susceptible to allergen penetration with basic formulations. In a 5-year follow-up study, no differences were found between groups altogether.[34] The use of basic level 1 emollients from birth does not prevent the development of AD, as exemplified by the BEEP trial[33] and the 5-year follow-up study using the level 1 emollient.[34]

In contrast, an RCT on daily use of high-risk infants of level 3 emollient, from birth to two months, reduced AD incidence at 12 months,[35] and yet another RCT showed that twice-daily prophylactic use of level 3 ceramide-containing moisturizer may

prevent the development of food sensitization better than daily application of basic level 1 emollients used in previous trials.36 The recent CASCADE AD prevention trial included daily application of three level 3 ceramide-containing emollient creams, which significantly reduced the prevalence of AD at 1 year.[37] The researchers suggested that daily application of the 3 ceramide-containing emollient creams may be a feasible approach in the US to reducing the AD burden.[37]

In addition to emollients, the use of gentle, soap-free wash products in AD should also be addressed. An RCT demonstrated a positive effect on treatment outcomes in mild-to-moderate AD after 4 weeks of using a gentle ceramide-containing wash product instead of a regular soap bar, particularly when both a gentle wash product and a level 3 emollient were used.[38]

An appropriately formulated mild wash product can be kind to the skin and effectively kill organisms such as COVID. An in vitro study showed that cholesterol and ceramide lipids facilitate fusion, suggesting that targeting these lipids could be effective against SARS-CoV-2, impeding the virus entry into the host cell.[39]

There is a lack of awareness of the choice of emollient level, despite the continuous development in emollients from simple to more comprehensive formulations. For example, in the UK, the majority of reimbursed emollients are level 1, while some available level 3 emollients are currently non-reimbursable.[29,30] The addition of further evidence with clinical trials may support specific recommendations on level 3 emollients, potentially justifying reimbursement of more comprehensive emollients for AD, specifically. To address this challenge, a study was conducted to investigate the effectiveness of comprehensive level 3 emollient formulations compared to basic level 1 formulations. The increasing evidence may support the additive benefits of recommending level 3 emollients and gentle, soap-free wash products for AD patients. It is expected that in April 2026, a ceramide-containing level 3 emollient will be reimbursed on the UK National Health Service (NHS).

Conclusively, an ideal emollient formulation is safe, effective, cost-effective, free from unnecessary additives, fragrance, and other sensitizing agents, optimizes SC lipid and water content, while being pleasant and acceptable to use for optimal patient satisfaction and concordance.

Statement 5. *Methods investigated to augment concordance with baseline skincare involved education, reminders, and frequent communication with patients given the following recommendations:*

a) Daily use of emollients, liberally and frequently as baseline treatment to delay flares and reduce symptoms
b) Skincare such as gentle wash products and emollients should not contain irritants and have a skin physiological pH (4-6)

To increase concordance with treatment recommendations, interventional tools for patient education are needed and should be prioritized.[13,15,24] Patient education should be provided in-clinic, in writing (eg, as AD action plans), and repeated at close follow-up visits, particularly at the beginning of treatment regimens.[16,26,27] Nurses are an excellent source of patient education as they can provide product information and give practical advice on application and routines.[7] Key education points to discuss with patients include the properties of an emollient and its role in AD management, specifically, and how to apply it correctly and in appropriate amounts.[23] Follow-up with patients should include noting the used quantity per week. In some cases, this can reveal underuse, which may explain suboptimal effect, while in severe AD cases, overuse of TCS may indicate a need for treatment change, including escalating to systemic treatment.[23] Inspired by other fields in medicine, patient education and actions plans could potentially be integrated in digital platforms such as educational applications, making it easy and available to patients to get continuous reminders of their treatment plan, and providing them with additional "on-the-go" follow-up and advice.[13,15,25]

Skincare products, including both emollients and mild emollient wash products, should be gentle, soap-free, not containing irritants, and approximate the physiological skin pH. However, while pH has gained increased focus, there is a lack of consideration of acid strength and buffering capacity in skincare products. Acidic products can shift the skin pH, which the skin's natural buffer systems will adjust accordingly. A functioning buffer system will keep the pH of skin optimal, crucial for ceramide synthesis, which requires a somewhat acidic environment. If the buffer system is weak, the pH of the skin will be unstable and dysfunctional. Considering the acidic buffering properties of a skincare product is more important than the pH in itself.

Limitations

The paper focuses on emollients for AD patients and their concordance with emollient use. The brief discussion of topical treatments is limited to current practice in Nordic European countries and therefore does not include topical phosphodiesterase 4 (PDE 4) inhibitors and Janus kinase (JAK) inhibitors.

CONCLUSION

Topical treatment is the cornerstone of AD management, but its effectiveness is highly dependent on long-term concordance. Studies suggest that the specific emollient properties are determinant, both regarding clinical effect and practicalities supporting concordance to a daily routine. Skincare recommendations need to be evidence-based, and increasing number of studies are showing that level 3 emollients are superior to less comprehensive formulations. Interventions, including patient education and more intelligent follow-up, have the potential to improve concordance and, thus, treatment outcomes.

DISCLOSURES

An educational grant from CeraVe Nordic European Countries supported the research for this work. The authors (MD, PB, AA, SK, CO, AW, GLG, and MJC) received fees for contributing to this work. All authors contributed to the development of the manuscript, reviewed it, and agreed with the final version. Authors declare no conflicts of interest with the manuscript content.

ACKNOWLEDGMENT

Hinke Andriessen (HA) assisted with the literature search.

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doi:10.36849/JDD.9880

October 2026 956 Volume 25 • Issue 10

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Off-Label Uses of Nemolizumab: A Narrative Review

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ABSTRACT

Background: Nemolizumab, a humanized monoclonal antibody targeting interleukin-31 receptor α (IL-31Rα), is approved for atopic dermatitis (AD) and prurigo nodularis (PN) in adults and pediatric patients 12 years and older, following phase 3 trials demonstrating significant reductions in pruritus and disease severity in patients inadequately controlled with topical therapies. Emerging evidence has demonstrated rapid and sustained pruritus reduction in diverse pruritic conditions beyond its approved indications.

Methods: We reviewed the literature from 2021 to 2025 examining off label nemolizumab use, analyzing case reports, case series, randomized controlled trials, and meta-analyses across dermatologic and systemic pruritic conditions.

Results: Across 16 studies with diverse diagnoses, nemolizumab demonstrated consistent efficacy in multiple off-label conditions including cutaneous amyloidosis, lichen simplex chronicus, uremic and dialysis-associated pruritus, cholestatic pruritus, and refractory dermatologic conditions. Adverse events were consistent with those described in its package insert.

Conclusions: Current evidence supports nemolizumab as a promising therapeutic option for treatment-refractory pruritic conditions. The rapid onset, favorable tolerability, and broad efficacy across conditions with elevated IL-31 signaling suggest significant clinical utility, though larger randomized trials are needed for definitive recommendations.

J Drugs Dermatol. 2026;25(10):956-961. doi:10.36849/JDD.9880

INTRODUCTION

Chronic pruritus remains one of the most challenging symptoms to manage across dermatologic and systemic conditions, significantly impairing quality of life and often proving refractory to conventional therapies. Nemolizumab represents a paradigm shift in treating chronic pruritic conditions through its targeted blockade of interleukin-31 (IL-31) receptor α signaling. IL-31, predominantly secreted by Th2 cells, type 2 innate lymphoid cells, and various immune effector cells, has emerged as a critical mediator in the pathophysiology of chronic itch across multiple disease states.[1]

Four pivotal phase 3 trials have studied nemolizumab in these conditions. The ARCADIA 1 and 2 phase 3 trials enrolled 1,728 patients, 12 years and older, with moderate-to-severe atopic dermatitis (AD). Patients were randomly assigned (2:1 ratio) to receive nemolizumab 30 mg subcutaneously every 4 weeks (Q4W) with a loading dose of 60 mg at baseline or placebo, both combined with topical corticosteroids (with or without calcineurin inhibitors) over a 16-week initial period. Both trials met their coprimary endpoints of Investigator's Global Assessment success and Eczema Area and Severity Index 75, with significant pruritus improvement observed as early as week 1 and sleep improvement by week 16.[1]

The phase 3 OLYMPIA 1 and 2 trials evaluated nemolizumab in a total of 560 adults with moderate-to-severe prurigo nodularis (PN). Both trials demonstrated significant improvements in primary and secondary endpoints, including rapid reduction in itch and sleep disturbance by week 4.[2] In OLYMPIA 2, which included 274 patients, 41.0% of those treated with nemolizumab achieved an itch response compared with 7.7% in the placebo group by week 4.

While nemolizumab has secured regulatory approval for AD and PN in patients 12 years and older, clinicians have begun exploring its utility in other IL-31-mediated pruritic conditions. This narrative review synthesizes the emerging evidence on off-label applications of nemolizumab, examining efficacy patterns, safety considerations, and mechanistic insights across diverse pruritic conditions to inform clinical decision-making and identify priorities for future investigation.

MATERIALS AND METHODS

We conducted a narrative review of the literature examining off-label uses of nemolizumab. We searched PubMed, Ovid Embase, and the Cochrane Library for English-language publications from 2021 through 2025 reporting original data on nemolizumab use for conditions other than approved indications (AD or PN in patients aged 12 years or older).

From each included study, we extracted data on study design, patient demographics, treated conditions, dosing protocols, prior therapies, outcome measures, and safety profiles. Our search was limited to English-language publications in major databases, potentially excluding relevant non-English studies and grey literature.

RESULTS

Our review identified 16 studies comprising 12 case reports, 1 case series, 1 randomized controlled trial, 1 systematic review, and 1 meta-analysis. These studies represented patients with 19 different diagnoses, with patient ages ranging from 7 to 90 years. The literature demonstrates a notable publication surge between 2023 and 2025, reflecting emerging clinical interest in off-label applications. Table 1 summarizes the key characteristics and findings of included studies.

Cutaneous Amyloidosis

Three case reports documented nemolizumab's efficacy in treating cutaneous amyloidosis. Nakagawa et al reported remarkable outcomes in a 39-year-old man with an 11-year disease history of lichen amyloidosis, who had failed topical steroids, antihistamines, and phototherapy.[3] Treatment with nemolizumab 60 mg Q4W for 2 years achieved pruritus resolution at week 6, with progressive morphologic improvement. At month 24, he had a near-complete lesion resolution with only mild residual elevation.

TABLE 1.

Summary of Included Studies on Off-Label Nemolizumab Use

Author, Year	Study Type	Condition	N (Age)	Dosing	Key Findings
Nakagawa 2025	Case report	Cutaneous lichen amyloidosis	1 (39y)	60 mg Q4W for 2 years	Pruritus resolved at week 6; near-complete lesion resolution at month 12
Fukumoto 2024	Case report	Primary localized cutaneous amyloidosis	1 (67y)	60 mg loading, 30 mg Q4W	Marked improvement after first dose; lesion flattening by month 4
Soto-Canetti 2025	Case report	Cutaneous amyloidosis	1 (44y)	60 mg loading, then 60 mg Q4W	Immediate relief within 5 days; marked improvement at month 2
Kinugasa et al 2021	RCT	Dialysis-associated pruritus	Multiple	0.125, 0.5, or 2.0 mg/kg, or placebo	Improvements by week 4; no clear difference vs placebo
Dalisay et al 2025	Case report	Uremic pruritus	1 (69y)	30 mg loading dose	Complete resolution (NRS 0) within 2 weeks; sustained month 8
Mima et al 2025	Case report	CKD-associated pruritus	1 (74y)	60 mg loading, then 30 mg Q4W	Complete resolution after 2 doses
Zhao et al 2024	Meta-analysis	Uremic pruritus	2,877	22 RCTs	Gabapentin ranked highest (69.74%) for pruritus relief, followed by cromolyn, hydroxyzine
Bai et al 2025	Systematic review	AD, PN, uremic pruritus	3,587 (313 UP patients)	30-60 mg Q4W vs placebo	Best response with 60 mg Q4W (26.6% vs 7.4% placebo)
Murase et al 2025	Case series	22 dermatologic conditions	Multiple	60 mg loading, then 30-60 mg monthly	96.3% continuation rate; 7.1% AEs
Ohmori et al 2023	Case report	Perforating dermatosis	1 (61 y)	Not specified	NRS 9→3 in 1 week; NRS 0 by week 8
Yamada et al 2024	Case report	Perforating collagenosis - vascular VEGFR inhibitor induced	1 (51y)	60 mg Q4W	Remarkable improvement after first dose; complete flattening of lesions within 4 months
Romanelli et al 2025	Case report	LABD	1 (67y)	30 mg monthly	Significant improvement in 1 week; sustained control at week 6
Soto-Canetti et al 2025	Case report	Cholestatic pruritus	1 (50s)	60 mg loading, then 30 mg Q4W	Complete resolution within 10 days; improved sleep
Masukane et al 2025	Case report	Post - Biliary Atresia surgery pruritus	1 (7 y)	30 mg of nemolizumab Q4W	Effective pruritus control achieved
Liszewski et al 2025	Case report	Scrotal dysesthesia	2 (29y, 33y)	60 mg loading, then 30 mg Q4W	Both cases: NRS 0 by week 12; resumed normal activities
Gruzmark et al 2025	Case report	Lichen simplex chronicus	1 (52 y)	Loading dose: 60 mg SC; maintenance: 30 mg SC Q4W.	Pruritus improved from 10/10 at baseline to 4/10 at 2 weeks, and to 0/10 after 2 months (4 injections), with improved sleep and quality of life; no AE reported.
Gruzmark et al 2025	Case report	Lichen simplex chronicus	1 (52 y)	Loading dose: 60 mg SC; maintenance: 30 mg SC Q4W.	Pruritus improved from 10/10 at baseline to 4/10 at 2 weeks, and to 0/10 after 2 months (4 injections), with improved sleep and quality of life; no AE reported.

Similarly, Fukumoto et al described a 67-year-old patient with a 20-year history of primary localized cutaneous amyloidosis and pediatric-onset AD.[4] He achieved marked pruritus improvement after the first nemolizumab dose, with lesion flattening by month 4 and a decrease in immunoglobulin E levels. He received 60 mg of nemolizumab Q4W in addition to ongoing topical treatment with Class II topical corticosteroids.

The third case, Soto-Canetti et al, involved a 44-year-old nonatopic man with lichen amyloidosis as early as 2006.[5] After trying dupilumab for 5 months at the PN-recommended dose, he had persistent pruritus with only mild improvement in the hyperkeratosis of cutaneous lesions. Dupilumab was discontinued and replaced with 60 mg Q4W based on the patient's weight. Within 5 days, he reported immediate relief of pruritus, and within 2 months he sustained resolution of symptoms as well as improved hyperkeratosis of cutaneous lesions.

Lichen Simplex Chronicus

Lichen simplex chronicus is a particularly challenging manifestation of chronic pruritus characterized by lichenified skin secondary to an intractable itch-scratch cycle. Gruzmark et al, 2025 reported a compelling case of lichen simplex chronicus in the setting of neuropathic pruritus successfully treated with nemolizumab in a 52-year-old woman with an 8-year history of severe labial pruritus.[6] The patient had a notable history of an L4-L5 disc bulge secondary to a motor vehicle accident 9 years prior, suggesting a neuropathic component to her pruritus. Her condition had proven refractory to intralesional triamcinolone, ketamine-amitriptyline-lidocaine formulation, silver sulfadiazine cream, and pramoxine hydrochloride lotion. She also attempted clobetasol/halobetasol, which provided some symptom relief but was discontinued due to atrophy risk.

Within 2 weeks of receiving a loading dose of 60 mg nemolizumab, followed by 30 mg Q4W, the patient's itch severity decreased from 10/10 to 4/10. By 2 months after treatment initiation and following 4 total injections, complete pruritus resolution (0/10) was achieved. The patient reported significant improvements in sleep quality and quality of life. She did not report any side effects.

Uremic and Dialysis-Associated Pruritus

An early RCT by Kinugasa et al demonstrated improvement in dialysis-associated pruritus by week 4 across all groups, including placebo, with no clear advantage for nemolizumab.[7] However, more recent case reports have documented dramatic individual responses. Dalisay et al, reported a 69-year-old hemodialysis patient who achieved complete pruritus resolution (numeric rating scalse (NRS) 0/10 from baseline 8/10) within 2 weeks of a single 30 mg loading dose, with sustained benefit over 8 months.[8] Prior to this, he had failed 6-week trials of triamcinolone acetonide 0.1% ointment, NB-UVB phototherapy, N-acetylcysteine and gabapentin. Similarly, Mima et al described a 74-year-old patient whose severe pruritus, peak pruritus numeric scale (PP-NRS) 9 to 10, resolved completely after the second dose of nemolizumab treatment, following inadequate control with difelikefalin, a κ-opioid receptor agonist.[9] He was given 60 mg at baseline, followed by 30 mg monthly.

Two reviews provided context for nemolizumab's position in the uremic pruritus treatment landscape. Zhao et al's 2024 network meta-analysis of 22 RCTs encompassing 2,877 patients found gabapentin ranked highest for pruritus relief (69.74%), followed by cromolyn sodium and hydroxyzine.[10] However, Bai et al's systematic review of 11 articles found that of the 313 uremic pruritus patients, 68.4% received nemolizumab and 31.6% received placebo.[11] Compared to placebo, nemolizumab showed the best responses at 60 mg Q4W for PP-NRS reduction, 26.4% vs 7.4% with placebo at week 4. The contrast between modest trial outcomes and striking individual responses suggests that certain patients may derive exceptional benefit from nemolizumab, even though overall population-level effects remain limited.

Diverse Dermatologic Conditions

The largest off-label study comes from Murase et al, 2025's multicenter series of 60 patients.[12] Patients in the study presented with a wide range of dermatologic and pruritic conditions, including AD, nummular/hand dermatitis, dermatographia/ urticaria, cutaneous mastocytosis, neuropathic itch, subacute prurigo, immunologic eruptions of aging, lymphoma/leukemia, scrotal/vulvar/ anal pruritus, acquired cutaneous brachioradial pruritus, notalgia paresthetica, scabies, postscabetic ID hypersensitivity, lichen amyloidosis, pernio, granulomatous dermatitis, neuropathic skin pain, burning mouth syndrome, neurogenic rosacea, and erythromelalgia.

All patients had exhausted conventional therapies, with 100% having failed topical or intralesional steroids, 98.6% having failed antihistamines, and 84.2% having failed systemic immunomodulators. After treatment with nemolizumab (60 mg loading dose, then 30–60 mg monthly), an impressive 96% of patients continued therapy due to meaningful improvement. Notably, acquired brachioradial pruritus showed no response (0%), while notalgia paresthetica demonstrated only partial efficacy (50%), potentially suggesting these specific neuropathic conditions may be less IL-31 dependent. Nemolizumab's safety profile remained favorable, with only 7.1% experiencing adverse events, nonsevere, supporting the medication's overall tolerability in heterogeneous patient populations.

A few isolated case reports demonstrated efficacy in other refractory conditions. Romanelli et al described a 67-year-old woman with linear IgA bullous dermatosis (LABD).[15] The patient experienced persistent severe pruritus affecting 30% of body surface area. She had previously failed omalizumab, topical

ruxolitinib, intravenous immunoglobulin, and dupilumab. A monthly dose of nemolizumab 30 mg achieved significant improvement within 1 week and sustained itch control at week 6 (1/10 itch). She continued her existing regimen of IV rituximab 375 mg/m^2 every 3 months, mycophenolate mofetil 500 mg twice daily, and gabapentin 300 mg nightly while taking nemolizumab.

In another case, Soto-Canetti et al reported complete pruritus resolution within 10 days in a patient with recurrent primary sclerosing cholangitis and 2 liver transplants.[16] This patient had experienced minimal relief from hydroxyzine, naltrexone, pramoxine, and dupilumab. At the time of publication, he continued to take nemolizumab and sustained an average itch NRS of 0. He had 2 instances of missed maintenance dosing that resulted in recurrence of pruritus symptoms, which fully resolved once he restarted nemolizumab.

A pediatric case by Masukane et al reported a pediatric case involving a 7-year-old patient.[17] The patient achieved effective pruritus control after receiving 30 mg of nemolizumab Q4W for a total of 5 doses over 4 months. The pediatric patient's pruritus was well controlled with nemolizumab and ursodeoxycholic acid at the time of publication. Finally, Liszewski et al reported 2 cases of scrotal dysesthesia treated with nemolizumab.[18] Complete symptom resolution was achieved by week 12. Patients were able to discontinue systemic medications and resume complete normal activities, including physical exercise and sexual function.

Perforating Dermatoses

Two cases of acquired reactive perforating collagenosis (ARPC) demonstrated both pruritus and lesion resolution with nemolizumab. Ohmori et al reported a hemodialysis patient whose NRS decreased from 9 to 3 within 1 week of initiating 60 mg nemolizumab administered Q4W.[13] At week 8, the NRS reached 0. A year later, he received NB-UVB phototherapy because his pruritus was worsening. At his 12-week follow-up, the NRS remained stable between 0 and 2, leading to discontinuation of nalfurafine and the frequency of phototherapy. Previous phase 3 trials demonstrated PN resolution at week 4, making this case's resolution in 1 week notable.[2]

Yamada et al discuss a case of drug-induced acquired reactive perforating collagenosis in a 51-year-old patient with lung cancer following VEGFR inhibitor treatment.[14] After experiencing no improvement despite discontinuing biologics for 2 months, nemolizumab 60 mg Q4W resulted in remarkable improvement in both pain and pruritus after the first dose and complete lesion flattening within 4 months.

Safety Profile

Overall, nemolizumab generally has a favorable side effect profile. In OLYMPIA 1, confirmed asthma worsening occurred in 3.2% of nemolizumab-treated patients vs 1.1% of placebo recipients.[19] All the events were mild-to-moderate, and none led to study discontinuation. In OLYMPIA 2, there was no treatment imbalance in asthma events.

The ARCADIA phase 3 trials revealed worsening AD as the most common AE (12% vs 11% in placebo in ARCADIA 1; 7% vs 6% in ARCADIA 2), though these events were reported per investigator judgment and without a consistent definition. The use of rescue therapy was lower among the nemolizumab group.[1] Confirmed asthma exacerbation rates were 5% (ARCADIA 1) and 1% (ARCADIA 2) in nemolizumab groups, with no significant imbalance vs placebo. Approximately 30% of participants had baseline asthma. The incidence rates aligned with expected annual exacerbation rates in the general asthmatic population (approximately 40% of adults over 18).

DISCUSSION

Nemolizumab demonstrated significant antipruritic efficacy across multiple conditions. The strongest responses were observed in AD and PN, supported by robust evidence from multiple large, randomized controlled trials (RCTs) including over 3,000 patients. For off-label uses, uremic pruritus showed moderate evidence from controlled studies, though a recent network, Zhao et al's meta-analysis found insufficient data to draw definitive conclusions.[10] Other emerging off-label applications, including cholestatic pruritus, dialysis-associated pruritus, cutaneous amyloidosis, and perforating dermatoses, were supported by case reports and small case series.

High-quality RCTs establish nemolizumab as a highly effective therapy for inflammatory and pruritic disease. Specifically, ARCADIA 1/2 in AD and OLYMPIA 1/2 in PN demonstrate that nemolizumab provides rapid and sustained improvements in pruritus, skin lesions, sleep, and quality of life. Across these studies, benefits were observed early and maintained over time, confirming durability and a favorable safety profile. Together, these trials highlight the clinical relevance of IL-31 blockade, positioning nemolizumab as a well-tolerated, mechanism-based therapy that addresses the care drivers of disease in patients with difficult-to-treat pruritic skin conditions.

Beyond its current approved indications, nemolizumab demonstrated pruritus resolution across diverse and treatment-refractory pruritic conditions. In a multicenter prospective case series of 70 patients with diverse pruritic disorders, including atopic dermatitis, hand/nummular dermatitis, urticaria, cutaneous mastocytosis, neuropathic or systemic itch, prurigo, scabies-related eruptions, lichen amyloidosis, and other inflammatory, immunologic, or neuropathic dermatoses. Murase et al reported that 96% of patients chose to continue therapy due to sustained symptomatic improvement.[12] Numerous independent case reports further described rapid and significant responses in conditions traditionally difficult to

treat. Although these observations are based on individual case reports and smaller studies, their consistency across diagnoses and study settings supports the hypothesis that IL-31 represents a shared downstream pathway in chronic pruritus, regardless of underlying etiology.

While discussing the current literature surrounding off-label use of nemolizumab, several limitations should be acknowledged. The evidence currently includes predominantly case reports and small case series, which may overrepresent positive outcomes. While nemolizumab does have large phase 3 RCT data for AD and PN, RCT data for other pruritic conditions are still limited. A network meta-analysis of uremic conditions included nemolizumab alongside gabapentin but found insufficient data to draw a definite conclusion.[10]

Outcome measurement heterogeneity is another significant limitation. Pivotal phase 3 studies by Kwatra et al and Silverberg et al included validated instruments such as PP-NRS, Investigator's Global Assessment scale, Eczema Area and Severity Index and the Sleep Disturbance Numerical Rating Scale.[1,2] Throughout the literature, some case reports/case series used NRS while others used another 0 to 10 itch scale, Patient-Oriented Eczema Measure scores, or the Dermatology Life Quality Index (DLQI).

Another significant limitation is that no cost-effectiveness data have been gathered at this present time. More data are also needed to investigate the safety of using nemolizumab in the pediatric population. The study by Igarashi et al is the only long-term publication that follows patients 6 to 12 years of age with AD over 68 weeks of data in pediatric patients.[20] There has not been any data collected in patients under the age of 6.

Finally, the last major limitation to note is the lack of data on long-term nemolizumab use beyond 2 years. The study by Augustin et al outlines the safety and efficacy of AD up to 2 years, revealing that overall, 92.6% of adverse events were mild to moderate in severity.[21] A study looking at long-term nemolizumab use would be beneficial when treating chronic pruritic conditions. To optimize the selection of patients for nemolizumab therapy, future research can focus on identifying predictive biomarkers such as IL-31 levels, IL-31 receptor expression, and analyzing broad patterns of gene expression, which may provide a more thorough view of the patient's underlying pathology.

In summary, nemolizumab provides robust, rapid, and durable relief of chronic pruritus in AD and PN, with moderate evidence of uremic pruritus and growing support for efficacy across multiple refractory pruritic disorders. Future studies should focus on RCTs in systemic and neuropathic pruritus, biomarker-guided patient selection, pediatric expansion, and cost-effectiveness to better define its role in the evolving therapeutic algorithm for chronic itch.

CONCLUSION

This narrative review highlights emerging evidence for off-label use of nemolizumab across multiple pruritic conditions, often demonstrating symptomatic relief within 6 weeks. While phase 3 trials provide robust data for AD and PN in patients 12 years and older, evidence for other pruritic conditions remains limited to case reports and small case series.

Off-label applications may be considered in the treatment of refractory patients. With shared decision-making, clinicians can utilize past case reports and case series to help treat a variety of chronic pruritic conditions. Future research should focus on RCTs and comparisons to other alternative therapies, biomarker identification, and long-term safety and cost-effectiveness assessments to guide optimal patient selection.

DISCLOSURES

Alice B. Gottlieb has received honoraria as an advisory board member and consultant for Amgen, AbbVie, Biogen, BMS, Eli Lilly, Janssen, Novartis, Oruka, Sanofi, SunPharma, Takeda, Teva, and UCB.

Hermon Feron has no conflicts of interest or financial relationships relevant to this content to disclose.

Research funding: Alice B. Gottlieb has received research/educational grants from Bristol-Myers Squibb, Janssen, Moonlake, and UCB Pharma (all paid to Mount Sinai School of Medicine until May 1, 2025). At UTSW, she is Sub-I on studies from Janssen and BMS.

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doi:10.36849/JDD.10248

October 2026 962 Volume 25 • Issue 10

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Histological Analysis Shows That a Moisturizer Formulated for Dermatoporosis Increases Elastin Content and Improves Skin Elasticity

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ABSTRACT

Background: Dermatoporosis involves age-related alterations in dermal structure and cellular function, including changes in collagen, elastin, and markers of skin senescence. Changes in skin biomarkers (collagen I, elastin, senescence-associated beta-galactosidase, CD44, and CD47) were assessed following the use of a novel moisturizer, GC (Galderma Laboratories, L.P., Fort Worth, TX), by subjects with mature, aging skin.

Methods: This 12-week multisite study recruited female and male subjects aged 40 to 60 years of all races, ethnicities, and Fitzpatrick skin types. Subjects were required to have a history of fragile skin and dry, crepey skin on the knees. The GC cream was applied to the knee and thigh skin twice daily. A subset of 5 patients underwent 3-mm punch biopsies on the upper knee at baseline and week 12 for immunohistochemistry. Standardized photography of skin appearance and pinch-release tests were conducted at baseline and weeks 4, 8, and 12.

Results: With GC cream use, elastin expression increased from baseline to week 12 (18% to 36%; $P<.05$) and beta-galactosidase expression trended higher (18% to 24%). Expression of CD44 (91% to 92%), CD47 (81% to 82%), and collagen type I alpha 1 (94% at both timepoints) was stable. Subjects' skin firmness and appearance were visibly improved.

Conclusion: After 12 weeks of twice-daily use of the GC cream, there was a significant increase in elastin expression, which was accompanied by visual improvement in skin elasticity and texture. These data validate clinical histological findings and show how topical intervention can improve overall skin health.

J Drugs Dermatol. 2026;25(10):962-966. doi:10.36849/JDD.10248

INTRODUCTION

Dermatoporosis is an age-related condition characterized by progressive loss of the skin's mechanical strength and structural integrity.[1] It first presents as fragile skin with senile purpura, stellate pseudoscars, and skin atrophy, and can progress to skin lacerations, superficial or deep dissecting hematomas, and, in severe cases, skin necrosis.[1,2] Functionally, dermatoporosis is characterized by reductions in collagen, elastin, and glycosaminoglycans within the subdermal extracellular matrix, leading to decreased skin thickness and elasticity.[3,4] At the cellular level, mitochondrial impairment, reduced autophagic capacity, and accumulation of senescent cells are observed.[5]

Dermatoporosis predominantly affects sun-exposed skin, and it occurs in up to 37% of individuals aged 65 and older; women are more frequently affected than men.[2,6,7] Although prevalence is highest among older adults, skin fragility can be clinically relevant in individuals across a broad age range.[2] Additional risk factors include genetic susceptibility, chronic renal failure, anticoagulant use, chronic obstructive pulmonary disease, epidermal growth factor receptor inhibitor use, and physical inactivity.[8]

Despite its prevalence, the molecular mechanisms of dermatoporosis are not fully understood, and the biomarkers of dermatoporosis are poorly characterized.[9] On this basis,

several structural and senescence-associated markers have been identified as potential biomarkers of dermatoporosis.[9] CD44 is a cell-surface receptor that binds hyaluronic acid and contributes to epidermal homeostasis. Hyaluronate signaling through CD44 has been directly implicated in skin atrophy and dermatoporosis-related changes.[1,2,10] CD47 is a transmembrane protein classically recognized for its inhibitory signaling against phagocytosis and is a modulator of several aging-related processes.[5] CD47 expression is elevated in aged tissues and senescent cells, and it may be a potential novel biomarker for photoaging.[5,11]

Senescence-associated beta-galactosidase (SA-β-gal) is a widely used biomarker of cellular senescence in vitro and in aging skin, where its age-dependent induction reflects the accumulation of senescent fibroblasts and keratinocytes, and may be relevant to dermatoporosis.[12,13]

Together, CD47 and SA-β-gal provide complementary measures of senescence-associated cellular changes. Type I collagen is the most abundant fibrillar protein in the dermis, comprising 80% to 85% of the dermal extracellular matrix and conferring mechanical strength through its triple-helix structure.[14] Expression of collagen type I alpha 1 (COL1A1) declines measurably with age.[14] Finally, elastin (ELN) is responsible for the skin's elastic property. It has a very low rate of turnover, and its production ceases in adulthood, rendering it especially susceptible to cumulative damage over time.[4,15] Together, these molecules comprise a set of measurable candidate biomarkers that capture distinct aspects of skin aging and dermatoporosis-related changes.

Previously, we found that a novel compound designed with a combination of microdosed *Centella asiatica* and mandelic acid has synergistic antisenescence and anti-inflammatory actions.[16] This study evaluated the efficacy and safety of an investigational topical cream, GC (Galderma Laboratories, L.P., Fort Worth, TX), in subjects with mature, aging skin. Specifically, we assessed changes in skin biomarkers via immunohistochemistry and conducted photographic assessments to correlate underlying tissue-level changes with clinical changes observed at the skin surface.

MATERIALS AND METHODS

Subjects

This 12-week multisite study was conducted in the United States in accordance with Good Clinical Practice guidelines. Institutional Review Board (IRB) approval was obtained on July 30, 2025 (IRB ID: 14308; ClinicalTrials.gov number: NCT07398989). All subjects provided written informed consent.

Subjects were directed to apply the GC cream twice daily for 12 weeks. A supporting SPF moisturizer was also provided, and subjects were instructed to use it before sun exposure and to reapply as needed throughout the day. Subjects agreed to stop using current topical skincare products for the duration of the study.

The study recruited male and female subjects aged 40 to 60 years of all races, ethnicities, and Fitzpatrick skin types, with a self-reported history of fragile and easily bruised skin. Eligible subjects had mild-to-moderate skin crepiness, photodamage, and firmness on the skin of the knees and lower thighs, defined as a score of 3 to 6 on the modified Griffiths scale (0 = none; 9 = severe).[17]

Assessments

For assessment of biomarkers, 3-mm punch biopsies were performed on 5 subjects randomly selected from the full study population from a single clinical site at baseline and week 12. Following each biopsy, subjects returned 5 days post-procedure for wound examination and suture removal.

Tissue samples were fixed in 10% neutral buffered formalin, dehydrated, and cut into 5-micron thick sections. Two slides per biopsy were prepared, for a total of 8 sections per tissue sample for each target stain. Immunohistochemical staining for CD44, CD47, collagen I (COL1A1), SA-β-gal, and elastin (ELN) was performed using a Thermo Scientific Lab Vision Autostainer 480S. A digitally scanned image of each tissue section was captured at 40× magnification with a Leica Aperio digital scanning system. The images were analyzed with the Positive Pixel Count v9 algorithm using ImageScope software to assess the total positivity or sum of total positive pixels. Average pixel positivity per target and per timepoint were calculated, and statistical analysis (t-tests; $P<.05$) was performed to compare the average positivity in product-treated tissues with baseline tissues for each target and for each subject. Staining with hematoxylin and eosin (H&E) was also performed to assess skin structure.

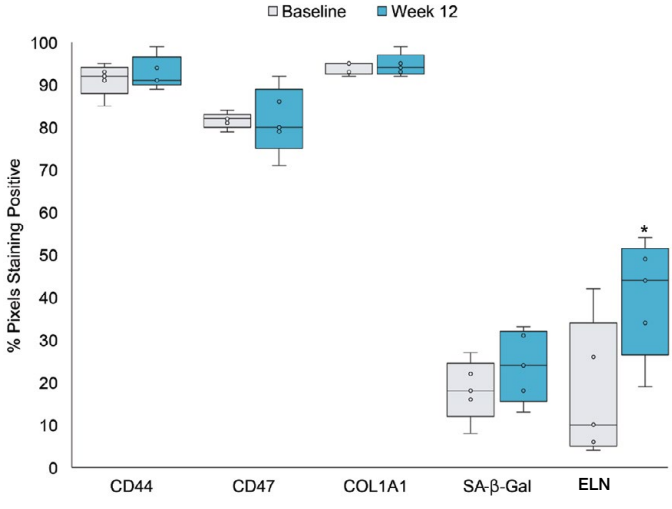
In addition to biopsy-based assessments, standardized clinical photography of the knees and lower thighs was obtained at baseline and weeks 4, 8, and 12 to document visible skin changes over time. Photography included neutral standing views and a standardized pinch-release maneuver at the upper knee to visually assess skin recoil and mechanical behavior. All images were captured under controlled positioning, lighting, and background conditions by trained study personnel.

Adverse events that occurred during the study period were monitored and reported.

RESULTS

A total of 31 subjects were enrolled in the study, ranging in age from 44 to 60 years. As previously described by Ablon et al, 71%

FIGURE 1. Biomarker changes from baseline across all subjects. Expression of CD44, CD47, COL1A1, SA-β-gal, and elastin was assessed by immunohistochemistry and quantified by pixel staining at baseline and week 12. Data shown are the mean, range, and interquartile range results for n=5 subjects. *P<.05 vs baseline.



COL1A1, collagen type I alpha 1; ELN, elastin; SA-β-gal, senescence-associated beta-galactosidase.

had Fitzpatrick skin types I to III and 29% had Fitzpatrick skin types IV to VI.[18] Five subjects from a single site were randomly selected to undergo punch biopsies. These subjects were a mean of 57.4 years of age (range, 55-60 years), 4 were female, and 1 was male. Three identified as White/Caucasian, 1 as East Asian, and 1 as West Asian. Two subjects identified as Hispanic or Latino, and 3 were not Hispanic or Latino. Two subjects had Fitzpatrick skin types I to III, while the other 3 had Fitzpatrick skin types IV to VI.

Immunohistochemical analysis of skin biopsy samples showed a significant increase in elastin expression from baseline to week 12 (18% to 36% pixels stained; P<.05). SA-β-gal showed a trend toward increased expression (18% to 24%), while expression of other proteins remained stable throughout the study, including CD44 (91% to 92%), CD47 (81% to 82%), and COL1A1 (94% at both timepoints) (Figure 1).

Individual changes in elastin expression were consistent with all 5 individuals, demonstrating a significant increase in the percentage of stained proteins from baseline to week 12 (10% to 19%, 6% to 49%, 4% to 44%, 26% to 34%, and 42% to 54%, respectively; P<.05). Representative histologic cross-sections showed increased elastin staining intensity and broader dermal distribution at week 12 compared with baseline, consistent with the observed increases in elastin-positive pixel percentages (Figure 2). In addition, H&E staining showed consistent dermal collagenization throughout the study, with preserved dermal

FIGURE 2. Increases in elastin expression from baseline to week 12. Elastin expression was assessed in biopsy samples from 5 subjects at baseline and week 12. Representative images of elastin immunostaining are shown for Subject 101 and Subject 104 (scale bar = 200 µm).

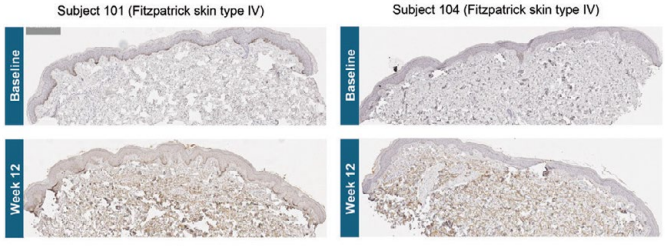
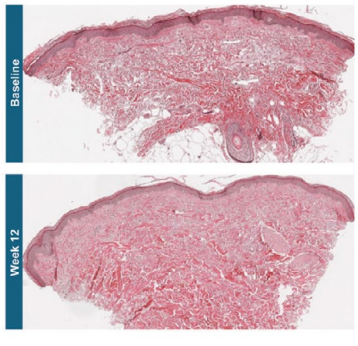


FIGURE 3. H&E staining for skin structure assessment. Skin structure was examined in H&E-stained biopsy samples from 5 patients at baseline and week 12. Representative images from Subject 103 (Fitzpatrick skin type II) are shown at baseline and week 12 (scale bar = 200 µm).



H&E, hematoxylin and eosin.

FIGURE 4. Pinch-release assessment. Skin recoil was assessed by pinch-release assessment at baseline and throughout the study. Representative responses to a pinch-release test are shown at baseline and weeks 4, 8, and 12 for Subject 106 (Fitzpatrick skin type II).

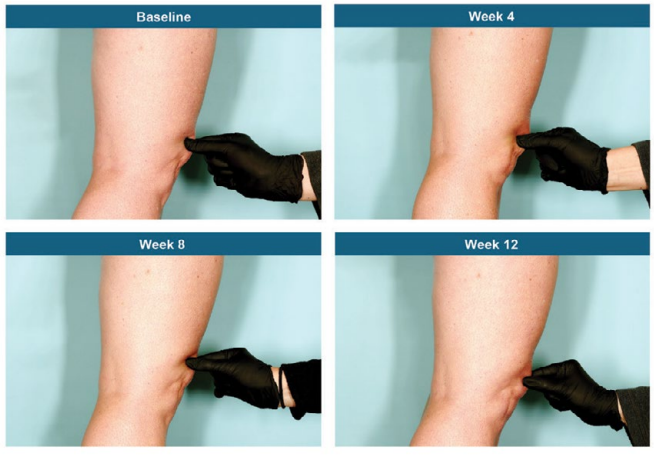
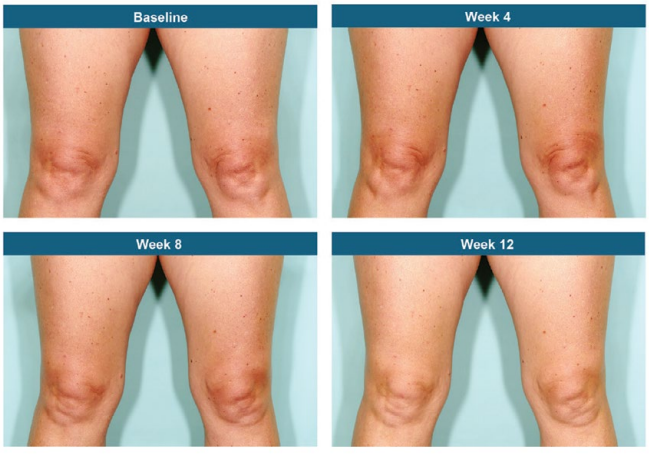


FIGURE 5. Clinical improvement in overall skin appearance and skin texture. Skin appearance was assessed using clinical photography at baseline and throughout the study. Representative results of changes in overall skin appearance and skin texture are shown at baseline and weeks 4, 8, and 12 for Subject 106 (Fitzpatrick skin type II).



architecture and no evidence of structural disruption (Figure 3).

Pinch-release assessments demonstrated improved skin recoil after 12 weeks of treatment with the GC cream, consistent with increases in subdermal elastin (Figure 4). Representative clinical photography demonstrated visible improvement in skin firmness and texture, with progressive changes observed from baseline through week 12 (Figure 5).

Thirty of 31 subjects completed the study, and there were no study product-related adverse events. The GC cream was well tolerated by all subjects, with no clinically meaningful increase in erythema, edema, or dryness at any post-baseline visit. Full safety and tolerability outcomes have been previously reported.[18]

DISCUSSION

This study shows that consistent twice-daily use of the GC cream for 12 weeks increased expression of proteins whose loss are associated with fragile, aging skin. The increase in elastin expression is of particular interest because of its contributions to skin elasticity, resilience, and structural integrity, all of which are at risk of decline in mature, fragile skin.[4,15] Subdermal elastin expression was accompanied by improvements in skin firmness and appearance, suggesting concordance between histologic changes and visible clinical outcomes. Qualitative improvements observed in standardized clinical photography, including visible reductions in skin crepiness and enhanced surface smoothness, were consistent with the biomarker-based evidence of improved dermal structural integrity.[1,2,4,7-9] In addition, the pinch test visually suggested progressive improvement in skin recoil over time, reflecting favorable changes in the skin's mechanical behavior that align with increased elastin expression.[1,2,8,15]

Limitations of this study include the small number of subjects who underwent biopsies and the relatively short study duration. Although the overall study enrolled 31 subjects, the biopsy analysis was limited to a subset of 5. While other exploratory biomarkers were generally stable over the 12-week study period, a larger sample size may identify additional, clinically relevant changes. Larger and longer studies are needed to further evaluate the effects of the GC cream on mature, fragile skin.

Notably, all 5 subjects who underwent biopsies demonstrated increased elastin staining from baseline to week 12. This subdermal tissue-level finding is directionally consistent with improvements in visible skin firmness on pinch-release assessment and overall skin appearance, supporting a cohesive interpretation in which external clinical improvements were accompanied by an underlying structural biomarker signal. Because elastin contributes to skin resilience and elasticity, the observed increase in elastin staining is biologically plausible and represents the clearest biomarker finding from this exploratory biopsy analysis.

CONCLUSION

These findings demonstrate that 12 weeks of twice-daily use of the GC cream increased dermal elastin expression beneath the skin surface and resulted in visible improvements in skin firmness, texture, and post-pinch appearance at the skin surface. Together with previously reported improvements in skin texture and hydration,[18] these findings support the GC cream as a moisturizer that may help improve skin health both below and at the skin surface in individuals with dermatoporosis-related changes to the skin.

DISCLOSURES

Glynis Ablon MD is an investigator and/or consultant for AbbVie, Almirall, Bausch, Benev, Beiersdorf, Church & Dwight, Eli Lilly, Estee Lauder, Everwell, Galderma, La Roche-Posay, L'Oreal, Nutrafol, Omnilux, Revision, and Valensa. Todd Schlesinger MD has been an investigator and/or consultant for: AbbVie, Almirall, Apogee, Arcutis Biotherapeutics, Beiersdorf, Benev, Biofrontera, Bristol Myers Squibb, Crown Aesthetics, Dermsquared, Eli Lilly, Estee Lauder, Flint Clinical, Galderma, Genentech, HTL Biotechnology, Janssen, LaRoche Posay, LEO Pharma, L'Oreal, MJH Life Sciences, Oruka, Pfizer, RBC Consultants, Regeneron Pharmaceuticals, Sun Pharma, Verrica, and UCB; has served as an investigator for AbbVie, Allergan, Almirall, Arcutis Biotherapeutics, Aslan Pharmaceuticals, Biofrontera, Bristol Myers Squibb, Boehringer Ingelheim, Cara Therapeutics, Castle Biosciences, Concert Pharmaceuticals (acquired by Sun Pharma), Cutanea Life Sciences, Dermavant Sciences, Eli Lilly, Galderma, HighlightII, Incyte, Janssen, Nimbus Therapeutics, Medicus, Novartis, Processa, Prolacta, Regeneron Pharmaceuticals, Sanofi, SkinCure Oncology, Takeda, Trevi Pharmaceuticals, and

Verrica; is a shareholder of Bristol Myers Squibb, Chronicle Medical Software, Eli Lilly, and Remedly; and receives a salary from Avant-Health. Christine Emesiani PharmD, Sindhu Garimella MS, Thu Q. Nguyen PhD, Jean Philippe York PhD, Alan Widgerow MBBCh MMed, and Matthew Meckfessel PhD are employees of Galderma Laboratories, L.P.

Sources of Financial Support

Funding for the medical writing and editorial support of this manuscript was provided by Galderma Laboratories, L.P.

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US-CET-2500063 08/25

doi:10.36849/JDD.9619

October 2026 968 Volume 25 • Issue 10

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CASE REPORT

Journal of Drugs in Dermatology

Pulsed Dye Laser for Sensory Dysesthesias Associated With Chronic Radiation Dermatitis

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ABSTRACT

Chronic radiation dermatitis (CRD) is a long-term complication of radiation therapy, typically manifesting as scarred atrophic plaques with telangiectasias. In some cases, patients report persistent sensory dysesthesias such as burning, stinging, and pruritus. These symptoms are underrecognized and likely underreported but can significantly impair quality of life and are often refractory to conventional therapies. Pulsed dye laser (PDL) has demonstrated efficacy in treating CRD-associated telangiectasias, but its role in alleviating sensory symptoms has not been reported.

We report 2 breast cancer patients with treatment-resistant CRD and debilitating dysesthesias who experienced substantial symptom improvement following PDL therapy. The first patient presented with a decade-long nonhealing chest wall wound and refractory pruritus. She underwent 10 sessions of subpurpuric PDL at 6-week intervals, in combination with advanced wound care, and achieved complete wound healing and sustained relief of pruritus and skin fragility. The second patient presented with a burning erythematous axillary plaque present for 3 years. She underwent four PDL sessions at 5-week intervals and reported her first meaningful reduction in burning immediately after the initial treatment, with nearly complete resolution of dysesthesia by her final session despite persistent telangiectasias.

These cases suggest that PDL may offer a novel therapeutic option for CRD-associated dysesthesias, particularly when integrated with multidisciplinary care involving medical dermatology, laser specialists, and wound care. Larger, prospective studies are warranted to clarify PDL efficacy for CRD-related dysesthesias.

J Drugs Dermatol. 2026;25(10):968-970. doi:10.36849/JDD.9619

INTRODUCTION

Chronic radiation dermatitis (CRD) is a long-term complication of radiation therapy and usually presents as atrophic plaques with telangiectasias. In some cases, CRD can be associated with persistent sensory dysesthesias such as burning, stinging, and pruritus. These underrecognized and likely underreported symptoms can impair quality of life as they can cause discomfort, sleep disturbance, and emotional distress.[1] In many cases, they are refractory to conventional therapies.

Pulsed dye laser (PDL) has been shown to improve telangiectasias in CRD; however, its potential to relieve CRD-associated dysesthesias has not been reported. Similar to rosacea, where neurovascular dysregulation is thought to contribute to burning and stinging sensations, CRD-related dysesthesias may also have a similar pathophysiology. In this small case series, we describe 2 breast cancer patients with treatment-resistant CRD whose sensory dysesthesias improved following a series of PDL treatments.

CASE SERIES

Case 1:

A 63-year-old woman with Fitzpatrick skin type III and stage IIB invasive ductal carcinoma of the left breast underwent modified radical mastectomy and adjuvant radiation therapy. The first course delivered 50.4 Gy in 28 fractions to the left chest wall, with adjacent supraclavicular and medial parasternal regions each receiving 45 Gy in 25 fractions. Six years later, she received a second course of 50 Gy in 20 fractions to the sternum due to recurrence. Two years after her second treatment, she developed CRD with telangiectatic plaques and recurrent skin breakdown with a persistent non-healing wound. Her associated symptoms included pruritus. A biopsy was performed given persistent ulceration to rule out malignancy, which showed epidermal ulceration with mixed inflammation and focal cytologic atypia compatible with chronic radiation changes.

Over 7 years, she was evaluated at more than 50 dermatology visits and failed topical corticosteroids, calcineurin inhibitors, antifungals, doxepin, ruxolitinib, and intralesional triamcinolone.

FIGURE 1. (A) Chronic radiation dermatitis of the central chest prior to treatment, showing telangiectasias, erosions, and skin fragility. (B) Marked clinical improvement following ten sessions of 595-nm PDL, with reduction in skin breakdown, bleeding, and dysesthesia.



She was referred for PDL therapy due to persistent dysesthesias and refractory CRD. Ten sessions of 595-nm subpurpuric PDL were administered at approximately week 6 intervals (10 mm spot size, 20 ms pulse duration, and fluence of 4.0–5.0 J/cm^2 with cryogen cooling and non-overlapping pulses). Pulses were spaced to avoid bulk heating in fragile, previously irradiated skin.

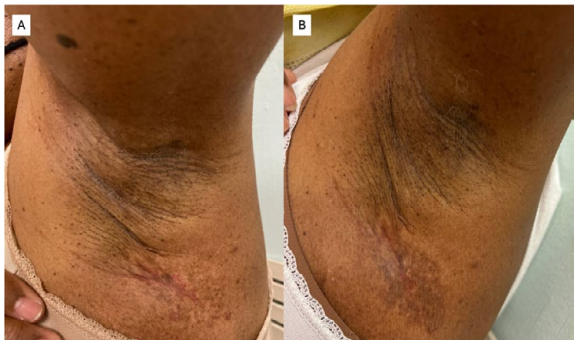
Following the first session, she reported reduced pruritus and less procedural discomfort than with intralesional corticosteroids. After her eighth PDL treatment, she was also evaluated by an academic advanced wound care center for a persistent but shrinking scabbed erosion, which improved with a bioactive wound matrix containing collagen, oxidized regenerated cellulose, and silver. Her main concern, which was the non-healing wound within the CRD that was persistent for 10 years, eventually healed completely by the tenth round of PDL and concurrent wound care (Figure 1).

Case 2:

A 73-year-old woman with Fitzpatrick skin type IV and a history of right breast ductal carcinoma in situ, previously treated with lumpectomy and adjuvant radiation, later developed stage IIB left breast cancer. She underwent lumpectomy and was followed by radiation, receiving 50 Gy in 25 fractions to the left breast and left supraclavicular region, with a 10 Gy boost to the lumpectomy cavity in 5 fractions. Four years post-treatment, she developed a persistent erythematous plaque in the left axilla with chronic burning and stinging. Biopsy confirmed chronic radiation dermatitis with dermal scarring and vascular ectasia. Over 3 years, she failed topical corticosteroids, tacrolimus, ketoconazole, and intralesional triamcinolone.

She underwent 4 sessions of 595-nm subpurpuric PDL therapy at approximately 5-week intervals (7–10 mm spot size, 10 ms pulse duration, and fluence of 5.0–7.0 J/cm^2).

FIGURE 2. (A) Chronic radiation dermatitis of the left axilla prior to treatment, with persistent telangiectasias and erythema associated with burning and stinging. (B) Clinical appearance after four sessions of 595-nm PDL with resolution of dysesthesia.



After the first session, she reported the first meaningful reduction in burning since symptom onset. By the fourth session, dysesthesia was mild and infrequent, and so she stopped treatment due to near resolution of her symptoms. On exam, telangiectasias persisted, but sensory symptoms had nearly resolved. She did develop post-inflammatory hyperpigmentation in the axilla (Figure 2) as an adverse effect of the PDL, but this was not bothersome to her given her drastic improvement in her dysesthesias.

DISCUSSION

These 2 cases suggest that PDL may offer a novel therapeutic option for managing sensory dysesthesias in CRD, particularly in patients who are unresponsive to conventional treatment. While the efficacy of PDL in treating radiation-induced telangiectasias is well-documented, its impact on dysesthesias has not previously been described. To our knowledge, this is the first report describing PDL as a potential treatment for sensory dysesthesia in CRD.

The mechanism behind PDL's effect on sensory dysesthesia in CRD is not fully understood, but may involve modulation of neurovascular and neuroimmune pathways, similar to those proposed in rosacea. In rosacea, burning and stinging sensations are thought to be mediated by neurogenic inflammation, driven in part by activation of transient receptor potential (TRP) channels such as TRPV1 and TRPA1 on sensory neurons.[2] These channels respond to thermal, chemical, and inflammatory stimuli, triggering the release of neuropeptides like substance P and calcitonin gene-related peptide (CGRP), which drive vasodilation, mast cell degranulation, and hypersensitivity of the skin. In rosacea, this neurovascular dysregulation is increasingly recognized as a key driver of sensory symptoms. Although less studied in CRD than in acute radiation dermatitis, radiation-induced tissue injury may also disrupt cutaneous innervation and vascular function,[3] potentially creating a comparable environment of neural sensitization. PDL, in addition

to its vascular-targeting properties, has been shown to reduce local inflammatory mediators and may attenuate this cycle of neurogenic inflammation, contributing to symptom relief.[4,5]

These cases also highlight the importance of recognizing CRD in patients with skin of color, in whom erythema and telangiectasias may be less apparent. In such patients, sensory symptoms like burning, stinging, and pruritus may be the most prominent clues to diagnosis. These differences, along with limited representation in existing studies, may contribute to diagnostic delays and undertreatment.[6]

Limitations of this report include the limited number of patients in the case series, retrospective design, and reliance on subjective patient-reported outcomes. In addition, no validated symptom severity scale was used, and long-term durability of symptom improvement remains unknown. Nevertheless, the marked symptom improvement in both patients after years of treatment resistance proposes further clinical utility of PDL for CRD-related dysesthesias, which has great potential benefit with limited adverse effects. Larger studies would help to clarify the efficacy of PDL for CRD-associated dysesthesias.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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doi:10.36849/JDD.9957

October 2026 971 Volume 25 • Issue 10

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CASE REPORT

Journal of Drugs in Dermatology

Cicatricial Ectropion in the Setting of IL-13 Inhibition

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ABSTRACT

Introduction: Interleukin (IL)-13 is a key mediator of type 2 inflammation and an important therapeutic target in atopic dermatitis (AD). Although IL-4/IL-13 and IL-13 inhibitors demonstrate favorable safety profiles, ocular adverse events are recognized complications. Conjunctivitis is most commonly reported, and cicatricial ectropion has been described with IL-4/IL-13 inhibition. We report what is, to our knowledge, the first reported case of cicatricial ectropion associated with inhibition of soluble IL-13.

Case Presentation: An 81-year-old man with longstanding AD involving 60% body surface area was treated with dupilumab with marked improvement. Seven months later, he developed ocular pruritus and tearing and was diagnosed with atopic keratoconjunctivitis. One month later, ophthalmologic examination revealed inferior cicatricial ectropion of the left lower eyelid. Discontinuation of dupilumab and treatment with oral prednisone and topical tacrolimus led to resolution. Subsequent treatment with tralokinumab resulted in recurrence of cicatricial ectropion within one month, prompting discontinuation and treatment with topical polymyxin B-trimethoprim and oral prednisone. Upadacitinib was initiated with sustained clearance of AD and no recurrence of ocular symptoms.

Discussion: Cicatricial ectropion has been rarely reported with dupilumab but has not previously been described with soluble IL-13 inhibition. In this case, ectropion developed with dupilumab, resolved after discontinuation, and recurred with tralokinumab, suggesting a direct effect of IL-13 inhibition. This case highlights the need for awareness of rare ocular complications associated with targeted therapies for AD and underscores the importance of multidisciplinary management.

J Drugs Dermatol. 2026;25(10):971-973. doi:10.36849/JDD.9957

INTRODUCTION

Inhibition of interleukin (IL)-13, a key mediator of type 2 inflammation, is a highly effective and targeted therapeutic strategy for atopic dermatitis (AD).[1] Despite an excellent safety profile, ocular adverse effects are a relatively common cause of treatment discontinuation.[1] Here we describe what is, to our knowledge, the first reported case of cicatricial ectropion associated with soluble IL-13 inhibition.

Case Report

An 81-year-old man presented for evaluation of a widespread rash present intermittently since childhood. His history was notable for seasonal allergies and ocular history of cataracts, dry eyes, and epiphora. At the time of evaluation, he was not receiving treatment, although he had previously used multiple topical corticosteroids. Examination revealed eczematous patches and plaques involving 60% body surface area (BSA) and Investigator Global Assessment (IGA) 3, prompting initiation of dupilumab at standard dosing (600 mg loading dose followed by 300 mg every two weeks). Seven months after initiation, he developed pruritus and tearing of both eyes without pain or visual changes. Examination revealed few eczematous papules and plaques involving the scalp, trunk and extremities, BSA 3% and IGA 1, overall, much improved from prior examinations. Ophthalmologic exam showed bilateral upper and lower lid edema and erythema with injection of the left conjunctiva. Ophthalmology diagnosed atopic keratoconjunctivitis and advised the patient to use lubricating and antihistamine eye drops.

FIGURE 1. Cicatricial ectropion of the left lower eyelid.



Repeat ophthalmologic evaluation one month later revealed cicatricial ectropion of the left lower eyelid (Figure 1). Treatment was initiated with tacrolimus ointment and oral prednisone (20 mg with a three week taper). Dupilumab was discontinued, and at re-evaluation three weeks later, the ectropion had resolved.

Nemolizumab (60 mg loading followed by 30 mg every 4 weeks) was initiated for AD but was discontinued one month later due to worsening AD without recurrence of ectropion. The patient was transitioned to tralokinumab at standard dosing (600 mg

FIGURE 2. Improvement of cicatricial ectropion after discontinuation of biologic and treatment with prednisone.

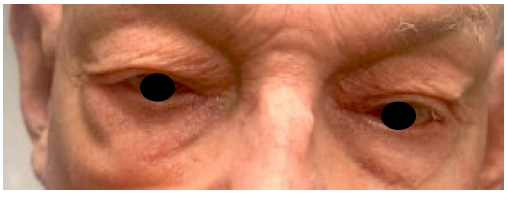
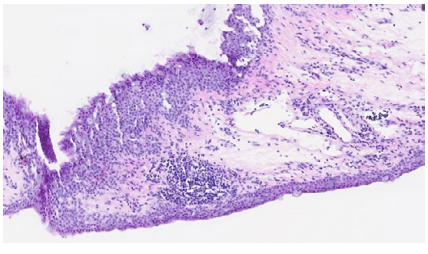


FIGURE 3. Hematoxylin and eosin (H&E)-stained section from biopsy of the left conjunctiva with high power view demonstrating focal fibrosis and chronic inflammatory infiltrate.



loading followed by 300 mg every 2 weeks). Within one month, his AD had improved, but cicatricial ectropion recurred and tralokinumab was discontinued. He was treated with topical polymyxin B-trimethoprim twice daily and a 3-week course of oral prednisone 20 mg daily.

Serologic testing and eyelid margin biopsy were performed to exclude mucous membrane pemphigoid or cicatricial pemphigoid. BP 180 and BP230 IgG, desmoglein 1 and 3 IgG, and anti-laminin 332 IgG were negative. Biopsy was notable for sub-epithelial fibrosis compatible with scarring and mild chronic conjunctivitis of the left conjunctiva (Figure 3). Direct immunofluorescence was negative. Age-appropriate malignancy screening was up to date. Upadacitinib 15 mg daily was initiated. At a follow-up visit one month later, improvement in ectropion was noted (Figure 2), along with significant improvement in his AD. At seven months follow up, the patient's AD was clear without recurrence of ocular symptoms.

DISCUSSION

Dupilumab, a human monoclonal IgG4 antibody targeting the IL-4 receptor alpha, inhibits IL-4 and IL-13, and is FDA-approved for the treatment of moderate-to-severe AD. Although generally well tolerated, treatment is associated with ocular adverse events, most commonly conjunctivitis and rarely cicatricial ectropion.[1,2-4] AD patients also have higher baseline rates of atopic conjunctivitis.[5]

Across dupilumab clinical trials for AD, there was a greater incidence of atopic keratoconjunctivitis compared to placebo, a pattern not observed in the trials for asthma, eosinophilic esophagitis, or nasal polyposis.[5,6,7] Although ectropion was not reported in early trials, it has since been described in case reports and in a multicenter retrospective study of 210 dupilumab-treated patients, in which cicatricial ectropion occurred in 1% of patients.[2-4,8] Conjunctivitis has also been reported with tralokinumab and lebrikizumab, monoclonal antibodies targeting soluble IL-13, though at lower rates than seen with dupilumab treatment.[1,9,10] Cicatricial ectropion has not been reported with these agents.[1,9,10]

To our knowledge, this is the first reported case of ectropion with soluble IL-13 inhibition.[11] Ectropion developed after exposure to dupilumab, resolved after discontinuation, and recurred with tralokinumab, before again resolving after drug discontinuation. This temporal pattern strongly supports a direct effect of IL-13 inhibition.

IL-13 contributes to ocular surface homeostasis by promoting goblet cell differentiation and proliferation and by upregulating genes involved in epithelial barrier integrity.[12] However, the mechanisms underlying ocular complications associated with therapies targeting IL-13 remain incompletely understood. Notably, higher baseline AD severity has been associated with increased conjunctivitis incidence, suggesting that longstanding, severe inflammation can contribute to disease pathogenesis.[5]

Cicatricial ectropion is characterized by outward eversion of the eyelid margin due to shortening of the anterior lamella secondary to scarring or contracture of the skin and subcutaneous tissue.[13] Previously reported cases of dupilumab-associated cicatricial ectropion occurred within 2-6 months of first exposure.[2,3,4] Treatment included discontinuing dupilumab, topical and oral corticosteroids, and topical calcineurin inhibitors.[2,3,4] In cases of drug induced ectropion, early drug discontinuation is critical.[14] In our patient, both episodes of cicatricial ectropion resolved following cessation of the implicated biologic and initiation of systemic corticosteroids, with active inflammation presumably controlled before clinically significant fibrosis developed.

This case expands our understanding of ocular adverse effects associated with IL-13 inhibition, independent of IL-4 receptor alpha blockade. It also underscores the importance of prompt recognition of targeted therapy-related adverse effects and the role of multidisciplinary care in optimizing patient outcomes. Further research is needed to clarify the ocular effects of IL-13 blockade.

DISCLOSURES

AC has received payments for conducting clinical trials (paid to her institution) from Eli Lilly, Incyte, Johnson & Johnson, Moonlake, Novartis, Merck and AbbVie; speaker fees from

Sanofi and Almirall; and consulting fees from Galdema, Eli Lilly, Oruka, CeraVe, UCB, Sanofi, Apogee, Veradermics, Incyte, Novartis, LEO Pharma, Almirall, Botanix, Bristol Myers Squibb, Fre Skincare, and Castle Biosciences. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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doi:10.36849/JDD.9852

October 2026 975 Volume 25 • Issue 10

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BRIEF COMMUNICATION

Journal of Drugs in Dermatology

Post-Inflammatory Hyperpigmentation in Skin of Color Patients With Atopic Dermatitis

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INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory condition affecting an estimated 129 million patients worldwide.[1] The chronic relapsing disease is characterized by recurrent, spongiotic patches with ill-defined borders and persistent, intense pruritus. AD often presents in early childhood and frequently persists into adulthood, significantly impacting quality of life. Chronic complications may resemble other dermatologic conditions, including seborrheic dermatitis, ichthyoses, plaque psoriasis, and pityriasis rosea.[2] Accurate diagnosis requires thorough history taking and differential diagnoses consideration, supported when necessary by skin biopsy.[3] AD-induced hyperpigmentation, especially in higher Fitzpatrick skin types, is an underrecognized complication where patients routinely mistake pigmentary changes for persistent active disease, with significant clinical and psychosocial impact.

Post-inflammatory hyperpigmentation (PIH) in AD is a sequela that results from the chronic inflammation underlying AD. Few publications describe in detail the characteristic findings, duration, psychosocial impact, and the response to chronic pigmentary changes, even when new medications are administered. Recently, a case report focused on the reduction of PIH in one adult skin of color (SoC) patient with AD treated with dupilumab.[4] Beyond AD, the VISIBLE study in psoriasis demonstrates the feasibility of intentional trial designs that capture historically underrepresented patients and SoC-relevant outcomes, including pigmentary changes.[5,6]

Patients with AD across all age groups, ethnicities, and Fitzpatrick skin types can experience PIH. Compared to Caucasian patients, African American and Hispanic patients are disproportionately affected by AD, and the clinical presentation may be more severe.[7] SoC patients with AD are more likely to develop lichenification, prurigo nodularis, and "follicular lichenification" with firm papules or diffuse thickening with prominent skin markings.[8,9] SoC patients may be delayed in referral to dermatology due to masking of the erythema associated with AD, resulting in delayed diagnosis and disease progression.[10] Persistence of AD into adulthood is more common in children with SoC compared with non-Hispanic white children.[11] While genetic predisposition may play a role, a variety of socioeconomic, environmental, and health care factors consistently influence AD severity, persistence, and prevalence among SoC patients.[12]

The literature discussing AD patients of diverse sex, gender, race, and ethnicity has been historically lacking. Less than 5% of publications in multiple high-impact dermatology journals focus on SoC populations.[13] Underrepresentation leaves clinicians unprepared to manage AD in patients most affected by its severe manifestations. Additionally, current therapeutic guidelines for AD do not consider ethnicity despite important clinical differences.[14]

This discussion highlights the duration and distribution of AD-induced hyperpigmentation in higher Fitzpatrick skin types. PIH has been underappreciated in the medical literature, and these cases serve to emphasize its clinical significance, particularly in populations historically underrepresented in dermatologic research.

CASE PRESENTATION

This collection of cases illustrates PIH in a cohort of patients with AD aged 1 to 17 years, focusing on individuals with SoC. The pigmentary changes observed in this group varied both in morphology and in severity, with many of the hyperpigmented areas also manifesting lichen simplex chronicus.

Younger children (Figures 1-3) presented with scattered hyperpigmented macules and patches on the anterior, lateral, and posterior lower extremities. Hyperpigmentation persisting longer than the original spongiotic dermatitis was observed in each of these cases. Other areas with pigmentary changes included the dorsal hands and upper extremities.

Adolescents (Figures 4-6) exhibiting PIH on the upper and lower extremities. The hyperpigmented areas tend to be larger and more confluent than those in the younger cohort, often corresponding to regions of chronic AD involvement. A greater number of plaques related to the duration of chronic inflammatory changes in adolescents are seen compared to those plaques illustrated in the younger age groups.

FIGURE 1. One-year-old female patient with PIH on bilateral lower extremities.



FIGURE 2. Seven-year-old female patient with PIH on dorsal hands and knees.



FIGURE 3. Ten-year-old male patient with PIH on bilateral upper extremities.



In all age groups, PIH persisted long after the resolution of the acute AD skin manifestations. Among these patients, the darker pigmentation lasted for months to years, depending on the chronicity and severity of the initial inflammation.

DISCUSSION

PIH is a concern in patients with SoC who suffer from AD, as the complication often leads to prolonged discoloration and considerable psychosocial impact. This case series demonstrates the protracted nature of PIH in SoC patients, with color changes persisting after the resolution of the acute phase of AD. The cosmetic and psychological burden associated with

FIGURE 4. 15-year-old female patient with PIH on bilateral upper and lower extremities.



FIGURE 5. 15-year-old female patient with PIH on bilateral lower extremities.



FIGURE 6. 17-year-old female patient with PIH on bilateral upper extremities.



PIH, especially in visible areas such as the face, neck, and hands, can lead to significant distress in these patients.[15] Addressing the pigmentation component in SoC patients with AD should be a priority in AD-focused research and provider treatment plans. Purposefully designed prospective trials such as VISIBLE provide a framework for representation and skin tone-relevant outcome assessment that could be applied to AD.[5,6]

Recent advances in the use of biologics, such as dupilumab and lebrikizumab, offer promising options for controlling AD as well as potentially mitigating the duration of PIH. Dupilumab, an IL-4 receptor antagonist, has been shown to reduce AD flares significantly and may help decrease the inflammatory triggers that lead to hyperpigmentation in SoC patients, as demonstrated in a single case report from 2020.[4] Similarly, lebrikizumab, a novel selective IL-13 inhibitor that binds IL-13 and inhibits signaling via IL-13Rα1 while preserving binding to IL-13Rα2, a decoy receptor implicated in IL-13 clearance, has demonstrated improved outcomes of PIH in AD patients, with 64.4% of patients (n = 45)

showing improvement in hyperpigmentation after 24 weeks of therapy in a phase IIIb trial.[16] This was the first AD clinical trial with a validated scale for both hypo- and hyperpigmentation being employed as an exploratory endpoint. While current data on targeted inhibitors and AD pigmentary outcomes are limited, these findings suggest that systemic therapies could shorten the duration or lessen the severity of PIH in AD. This case series highlights the phenomenon of PIH in SoC patients with chronic AD, underscoring the need for targeted treatment strategies that address residual hyperpigmentation.

Alternative studies have focused on early intervention and management of AD to reduce long-term disease burden. Practices such as early patient education, skin care regimens including moisturization, acute and chronic medical management, and aggressive prevention of inflammatory outbreaks have been associated with improved outcomes in SoC patients with AD.[17] Additionally, objective measures such as the PDCA-derm scale are validated and available for evaluating post-inflammatory dyspigmentation in AD to assist in recognizing the condition in patients of varying skin color.[18] Patients of varying skin tones present differently with post-inflammatory hyperpigmentation or hypopigmentation, and early recognition is paramount to ensure early intervention and prevention of complications.

Patients with PIH exhibit significantly higher psychosocial distress. In a study comparing the Dermatology Life Quality Index among patients with pigmentation disorders, patients with PIH were the most negatively affected cohort.[19] When considering treatment for AD, it is crucial to account for the entire clinical course of the condition, including the long-term burden of disease, local versus systemic manifestations, and psychological impact. Treating AD requires clinical context beyond managing local flaring and intermittent lesions. These cases highlight PIH as an often-overlooked complication in AD and suggest that a limited number of available biologic agents have been shown to improve PIH in SoC patients.

DISCLOSURES

There are no potential perceived conflicts of interest, support, or financial interests for Hayden Schandua. Dr Jafari has served or serves as an investigator for Arcutis, Dermavant, Amgen, Lilly, Nektar Therapeutics, Pfizer, Incyte, Janssen, and Sanofi. Dr Hebert has received research grants paid to UTHealth McGovern Medical School-Houston from Arcutis, Dermavant/Organon, Brickell Biotech, Galderma, LEO Pharma, Lilly, Mayne Pharma, Ortho Dermatologics, and Pfizer; has received honoraria from Almirall, Arcutis, BMS, Galderma, Incyte, Janssen, LEO Pharma, Lilly, Mayne Pharma, Ortho Dermatologics, Pfizer, Verrica, and Vyne; and serves on data safety monitoring board for Bausch, GSK, Sanofi-Regeneron.

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doi:10.36849/JDD.9650

October 2026 978 Volume 25 • Issue 10

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LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

Differences in Atopic Dermatitis Comorbidity and Treatment Patterns by Race

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To the Editor,

Atopic dermatitis (AD) is known for a wide range of comorbid conditions. For example, studies have shown that AD is associated with atopic comorbidities such as asthma, rhinitis, and food allergy, as well as nonatopic comorbidities such as ocular, psychiatric, infectious, endocrine, autoimmune, and cardiovascular diseases.[1] Treatment patterns can help alleviate these comorbidities. Consistent evidence has revealed that socioeconomic, environmental, and health care factors influence AD prevalence and severity; these same contributing risk factors are more frequently experienced among racial and ethnic minority populations as a result of racial disparities.[2] As a result, we sought to assess whether there were racial differences in comorbidities and treatment patterns in patients with AD using a large representative cohort.

We accessed de-identified electronic health records from the TriNetX Research Network on May 2, 2025. This database comprises approximately 144 million patients from 102 participating healthcare organizations. Patients who were between 18 and 89 years old at the time of AD diagnosis (ICD-10: L20) were identified, yielding cohorts of 283,293 White and 81,534 Black or African American individuals.

Propensity score matching (1:1) was performed based on demographic and clinical covariates, including age at diagnosis, sex, ophthalmic disorders, psychiatric conditions, autoimmune diseases, cardiovascular conditions, infections, bone density disorders, and malignancies. These variables were selected based on previously reported atopic and nonatopic comorbidities associated with AD. After matching, both cohorts included 76,654 patients, with all covariates demonstrating standardized mean differences less than 0.1, indicating successful balancing.

We assessed differences in prescription patterns and healthcare utilization within one year of AD diagnosis using odds ratios (OR) with 95% confidence intervals. Among comorbidities, most racial disparities were clinically insignificant. However, we observed significantly increased odds of inflammatory bowel disease (IBD) among Black AD patients compared to White AD patients. Specifically, Black atopic patients had increased odds of ulcerative colitis compared to White atopic patients (318 vs 407, OR 1.28, $P<0.0001$) and Crohn's disease (380 vs 499, OR 1.31, $P<0.0001$.

Previous studies have demonstrated that individuals with AD have about a twofold increase in odds of having inflammatory bowel disease.[3] However, our findings reveal a racial difference within this AD-associated comorbidity. Studies have analyzed triggers for AD and IBD, including triggers such as air pollution.[4] Our findings likely reflect environmental risk factors that disproportionately affect low socioeconomic groups.[5] Additionally, we found that among treatment patterns, mean times to follow up were similar between cohorts (309 vs 308 days), while white patients were more likely to be treated with ruxlotinib (Table 1).

TABLE 1.

Odds of Treatment for Atopic Dermatitis Among Selected Therapies

	Odds Ratio	95 % CI Lower	95 % CI Upper	Risk Difference	95 % CI Lower	95 % CI Upper	*P*-value
Dupilumab	1.1	1.01	1.19	0	0	0	0.02
Ruxolitinib	1.6	1.27	2.01	0	0	0	<0.0001
Tacrolimus	1.1	1.03	1.18	0	0	0	0.01
UV Therapy	1.04	0.87	1.25	0	0	0	0.67
Glucocorticoids	0.88	0.84	0.92	-0.02	-0.03	-0.01	<0.0001

We revealed several important observations among comorbidities and treatment patterns, most notably among inflammatory bowel disease and prescription trends for newer medications such as ruxlotinib. Increasing access to newer treatment options can help increase the arsenal of medications available to physicians and patients, while reducing the disease burden of atopic dermatitis. Further research should explore the underlying biological, socioeconomic, and systemic factors contributing to the observed racial differences in comorbidities and treatment access.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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doi:10.36849/JDD.10305e

October 2026 e89 Volume 25 • Issue 10

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LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

Association Between Sodium-Glucose Cotransporter-2 Inhibitors and Vulvar Pruritus Without Vulvovaginal Candidiasis: A TriNetX-Based Analysis

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To the Editor,

Diabetes mellitus (DM) is associated with an estimated 20 to 30% prevalence of vulvar/anogenital pruritus, with various potential etiologies.[1,2] Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are increasingly prescribed for DM and increase urinary glucose excretion, possibly altering vaginal flora, which may contribute to vulvar pruritus (VP). Prior work has demonstrated increased incidence of vulvovaginal candidiasis (VVC) among patients treated with SGLT2i. Still, the overall incidence of VP without VVC in this population is unknown.[5] Therefore, we investigated whether SGLT2i use is associated with increased VP.

We performed a retrospective cohort study using the TriNetX US Collaborative Network, which aggregates de-identified electronic health records (EHR). Adult women (≥18 years) with type 2 diabetes mellitus (T2DM) (ICD-10: E11) were stratified by those continuously prescribed SGLT2i (dapagliflozin, empagliflozin, canagliflozin, ertugliflozin) and unexposed controls. Prior diagnosis of VVC (B37.3), general candidiasis (B37), lichen sclerosis (L90.0), psoriasis (L40), lichen simplex chronicus (L28.0), contact dermatitis (L23–L24), lichen planus (L43), unspecified dermatitis (L30.9), or menopausal disorders (N95) was excluded from both cohorts to minimize confounders of VP. The index event was defined as the first SGLT2i prescription (exposed) or T2DM diagnosis (controls). The primary outcome was VP (L29.2) within 1, 3, and 5 years after the index event.

Propensity score matching (1:1) balanced demographics, comorbidities, and medications. Risk estimates and Cox proportional hazards (CPH) models were generated.

We included 53,025 patients in each cohort; over 1, 3, and 5 years, we observed 46, 71, and 83 cases of VP in the SGLT2i cohort compared with 16, 26, and 34 cases among controls. Absolute risk of VP was 0.087% vs 0.030%, 0.134% vs 0.049%, and 0.157% vs 0.064% in the SGLT2i and control cohorts at 1, 3, and 5 years, respectively. Risk analysis demonstrated a significant association between SGLT2i exposure and VP with risk ratios of 2.88 (95% CI 1.63–5.08), 2.73 (95% CI 1.74–4.28), and 2.44 (95% CI 1.64–3.64) across the respective time points. In the CPH model, the index event remained significantly associated with increased risk (HR 1.85, 95% CI 1.532–2.224, *P*=0.0063), representing an 85% higher hazard relative to controls. The cumulative incidence of VP increased with a longer duration of SGLT2i exposure.

Candidiasis-related ICD-10 codes were excluded from our model due to insufficient frequency within the matched cohort. Given the well-established association between SGLT2i and VVC and the low number of candidiasis codes observed, we hypothesize that VVC may be under-reported in EHR datasets in patients presenting with VP.[3] The 1.5-fold increased risk of developing VP with the presence of yeast in the urine, with concomitantly

TABLE 1.

VP and Study Covariates Cox Proportional Hazard Results

Covariate	Hazard Ratio	Standard Error	*P*-Value	95% Confidence Interval
SGLT2i cohort vs controls	2.38	0.096	< 0.0001	(1.97, 2.88)
Sodium-glucose co-transporter 2 (SGLT2) inhibitors	1.85	0.095	0.0063	(1.53, 2.22)
Hemoglobin A1c	1.00	0.009	0.3417	(0.98, 1.02)
Yeast [presence] in urine sediment by light microscopy	1.52	0.440	< 0.0001	(0.64, 3.60)

Within 3 years of the index event, patients in the SGLT2i group were 2.38 times more likely to develop VP compared to those not on SGLT2i. Specifically, having SGLT2i in the record was associated with a 1.85-fold increased risk of VP. Hemoglobin A1c was not associated with VP although presence of yeast in the urine was associated with 1.52- fold increased risk.

doi:10.36849/JDD.10305e

October 2026 e90 Volume 25 • Issue 10

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no association seen with an increased hemoglobin A1c, points to a fungal mechanism behind VP in a large number of patients. This emphasizes the importance of vulvar cultures in clinical practice and future studies evaluating SGLT2i-associated VP. The possibility of microbiota alterations and non-candidal infections remains a potential etiologies for VP in patients on SGLT2i.[5] The persistence of itch in patients on SGLT2i should warrant further investigation to guide management in the case of non-candidal fungal infections that may be resistant to standard treatment.

Limitations include retrospective design, medication adherence, reliance on ICD coding, and potential underdiagnosis of vulvovaginal infection. Laboratory data evaluating urinary glucose levels were limited, resulting in insufficient statistical power to assess this variable. Severity of pruritus could not be assessed with EHR data. Nevertheless, our findings suggest a meaningful association between SGLT2i use and VP, warranting further investigation into management of VP in the patient population.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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doi:10.36849/JDD.9347e

October 2026 e91 Volume 25 • Issue 10

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LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

Assessing the Variability of Dermatologic Needs in American Indian/Alaskan Native Populations: A Single-Center Retrospective Analysis

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To the Editor,

American Indian/Alaskan Native (AI/AN) populations have been historically underrepresented in dermatologic research. Given that the term AI/AN encompasses over 574 federally recognized tribes with cultural, linguistic, genetic, and geographic differences, it is necessary to evaluate whether existing research accounts for this diversity.[1,2] There are few studies investigating common skin conditions affecting AI/AN, and the results vary between them. Some conditions that have been cited as prevalent in AI/AN patients are the following: dermatitis, folliculitis, pityriasis alba, skin neoplasms, postinflammatory hyperpigmentation, actinic prurigo, and hypertrophic scar formation.[1,3,4]

This study investigates whether the AI/AN at a single institution in Southern California follows the trends from previous studies. A retrospective chart review was performed with AI/AN patient encounters at Loma Linda University Department of Dermatology between 2010 and 2022. Inclusion was determined by the race indicated in the electronic medical record. Diagnoses were determined by ICD-10 codes from each encounter. The following ICD-10 codes were excluded from our results: Z79.899 (encounter for use of high-risk medication) and Z85.828 (history of skin cancer). To reduce inflation from follow-up or medication management, visits were filtered to only include initial consultations and office visits, leaving 3,515 encounters included in this study.

Neoplasm of the skin, seborrheic keratoses, lentigines, psoriasis, and nevi ranked as the top 5 diagnoses, respectively (Table 1). Surprisingly, folliculitis and pityriasis alba were only documented in 23 and 7 encounters, respectively. Hypertrophic scarring was documented in 20 encounters, and actinic prurigo was not seen in any encounter. Psoriasis being among the top 5 encounters was unexpected, as previous research indicates low prevalence in AI/AN.[3] This data supports the necessity to reassess the dermatologic needs of AI/AN to better guide management and care of these populations. Given the paucity of research regarding the prevalence of dermatologic diseases within AI/AN populations, these findings suggest additional studies are warranted to better characterize any potential tribal differences or other factors that may affect AI/AN patients seeking dermatologic care.[2] Important next steps are to promote recruitment of AI/AN into dermatologic studies and further assess the generalizability of previous research. The authors recommend future studies consider the complex history and ethical considerations involving research in AI/AN populations and take particular care to maintain trust within these resilient communities.

TABLE 1.

Top 10 Diagnoses		
Diagnosis (ICD-10 Code)	Number of Encounters	Percentage of Encounters (%)
Neoplasm of Skin (D49.2)	180	5.1
Seborrheic Keratoses & Dermatosis Papulosa Nigra (L82.1)	176	5.0
Lentigo (L81.4)	133	3.8
Psoriasis (L40.9)	127	3.6
Benign Nevi (D22.9)	114	3.2
Acne Vulgaris (L70.0)	112	3.2
Eczema (L30.9)	110	3.1
Postinflammatory Hyperpigmentation (L81.0)	94	2.7
Actinic Keratosis (L57.0)	92	2.6
Seborrheic Dermatitis (L21.9)	80	2.3

DISCLOSURES

Jasmine Hawkins and Janiene Luke MD have no conflicts of interest to disclose.

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October 2026 981 Volume 25 • Issue 10

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NEWS, VIEWS, AND REVIEWS

Can't Believe It Can Be Cryo'd: Beyond Conventional Applications of Liquid Nitrogen

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INTRODUCTION

Liquid nitrogen cryotherapy is widely used in dermatologic practice, most commonly for verrucae, molluscum contagiosum, seborrheic keratoses, actinic keratoses, and selected low-risk keratinocyte carcinomas.[1,2] It is inexpensive, portable, most often does not require injectable anesthesia, and, when used appropriately, provides good cosmetic results with minimal wound care.[1] Rapid freezing at rates exceeding -25°C per second induces intracellular ice crystal formation, disruption of cellular membranes and organelles, and osmotic injury related to extracellular ice formation. This primary cellular injury is followed by microvascular thrombosis, tissue ischemia, and delayed necrosis.[3,4,5]

There is a broad range of less widely recognized conditions for which cryotherapy has been used. These applications take advantage of biologic effects that extend beyond direct tissue destruction. Lower-intensity cryotherapy represents a distinct therapeutic approach. Often termed superficial cryotherapy or "cryostimulation," it is not intended to produce tissue ablation. Instead, its effects may be mediated by reactive vasodilation, improved microcirculation, and local immunomodulation.[6] This review examines the less common dermatologic uses of cryotherapy and evaluates the evidence supporting these applications.

Kaposi Sarcoma

Cutaneous Kaposi sarcoma (KS) is among the best-supported indications for cryotherapy and is included by the National Comprehensive Cancer Network as a local treatment option when performed by clinicians experienced in cutaneous cancer cryotherapy.[7] Freezing produces direct tumor necrosis and vascular injury, mechanisms that are particularly relevant to this highly vascular neoplasm. Cryotherapy may also promote tumor antigen release and dendritic cell presentation, providing a rationale for combination therapy with immune-stimulating treatments.[8]

In a series of 30 patients with 125 lesions, two 15- to 40-second freeze-thaw cycles administered over a mean of 3.2 sessions produced complete response without recurrence in 63% of patients.[9] More recently, a randomized, single-blind study of classic HIV-negative KS cases found a 100% reduction in lesion score with cryotherapy compared to 42.6% with pro-yellow laser treatment (P=0.008). The greatest benefit was observed in papular and plaque-type lesions.[10] Cryotherapy was associated with more blistering and delayed healing, while laser treatment was better tolerated. Combination treatment may further improve efficacy: cryotherapy followed by topical imiquimod resulted in complete resolution of 42 of 45 lesions (93%), although the median time to resolution was 30.5 weeks.[11,12]

Overall, cryotherapy appears to be an effective and accessible option for limited cutaneous KS, particularly for papular or plaque type lesions. Its principal limitations are blistering, delayed healing, and the need for repeated treatment, and the evidence supporting combination therapy remains limited to small clinical series.

Alopecia Areata

Superficial cryotherapy for alopecia areata (AA) appears to contradict conventional effects of cryosurgery. Although cryotherapy delivered at tissue-destructive intensities can induce alopecia, superficial application with shorter freeze durations may instead promote hair regrowth.[13] Proposed mechanisms include reactive vasodilation, improved perifollicular circulation, and modulation of follicular inflammation.[13,14] The largest available study is a 22-year retrospective review of 353 patients with AA, in which 60.9% achieved a clinical response to cryotherapy after 3 months.[14] Response was more likely among patients experiencing a first episode of AA and those treated at intervals of 2 weeks or less, while adverse effects were limited to mild pain and pruritus.[14] A more recent randomized trial of 75 patients with recalcitrant disease found good-to-moderate improvement in approximately 65% to 76% of patients across different freeze durations.[15] Although overall response rates did not differ significantly, greater mean improvement was observed with 8- to 10-second and 13- to 15-second cycles, leading the authors to suggest an 8- to 10-second freeze duration.[15]

Across 8 studies, approximately 60% of patients achieved hair regrowth, with efficacy generally comparable to topical or intralesional corticosteroids and potentially lower relapse rates in some cryotherapy groups.[16] These findings suggest that superficial cryotherapy may be a low-cost alternative for localized AA, particularly when corticosteroid injections are unavailable, contraindicated, or poorly tolerated. However, the evidence remains limited by heterogeneous protocols, predominantly retrospective study designs, and insufficient long-term follow-up.

Lichen Simplex Chronicus

Lichen simplex chronicus (LSC) is sustained by an itch-rub cycle that produces persistent lichenified plaques. Standard treatment relies on potent topical corticosteroids and behavioral measures, although recurrence is common when friction to the area persists. Superficial cryotherapy has therefore been studied as an adjunct in refractory disease. Rather than ablating a discrete lesion, brief freezing may reduce sensory nerve signaling and thin the hyperkeratotic epidermis, thereby improving lesion appearance and mitigating symptoms.[17]

A meta-analysis of 12 randomized trials involving 1,066 participants found that cryotherapy-containing regimens improved clinical response compared with conventional therapy alone (RR 1.25; P=0.005).[17] Importantly, the benefit was confined to combination regimens: cryotherapy added to topical treatment was effective,

whereas cryotherapy as monotherapy was not superior to other interventions.[17] These findings support superficial cryotherapy as an adjunct for localized, treatment-resistant LSC rather than a replacement for topical corticosteroids.

Prurigo Nodularis

Prurigo nodularis (PN) is a chronic neuroimmune dermatosis in which intensely pruritic nodules perpetuate neural and inflammatory signaling through an ongoing itch-scratch cycle. Lesion-directed cryotherapy may interrupt this cycle by reducing nodule burden and local sensory signaling.

Evidence is limited to a small intra-patient randomized study of 11 patients. A single session of two 5- to 10-second freeze cycles produced 75% to 100% clearance on the cryotherapy-treated side in all patients, compared with 3 patients treated with clobetasol.[18] Cryotherapy was preferred by 63.6% of patients.[18] Although these findings suggest that cryotherapy may rapidly improve individual lesions, the very small sample size and limited follow-up preclude conclusions about durability or broader efficacy. Cryotherapy is therefore best considered an adjunct for a limited number of recalcitrant nodules rather than a treatment for widespread disease.

Granuloma Annulare

Localized granuloma annulare (GA) is another inflammatory dermatosis that often resolves spontaneously; however, cryotherapy may be considered for persistent or cosmetically bothersome lesions. Lesion-directed freezing is thought to disrupt the granulomatous infiltrate and induce local tissue remodeling.[19]

In a prospective study of 31 patients, all treated lesions resolved after contact cryosurgery, with 80.6% clearance after a single freeze-thaw cycle.[19] Among the 11 patients followed for more than 2 years, only one experienced recurrence, and cosmetic outcomes were rated good or excellent in 90% of evaluable patients.[19] These findings, although limited, suggest that cryotherapy can produce durable clearance. Universal blistering and the risks of dyspigmentation and atrophic scarring further restrict its use, particularly in patients with darker skin phototypes.

Keloids

Cryotherapy has been adapted as a fibrolytic treatment for keloids, where controlled freezing promotes vascular injury, necrosis, and collagen remodeling. Technique influences efficacy: intralesional cryotherapy generally achieves greater improvement with fewer sessions than spray or contact methods.[20]

Cryotherapy is most commonly used as part of combination therapy. Cryotherapy followed by intralesional triamcinolone reduced scar volume by 34.3% and height by 41.3% after 4 monthly treatments.[20] In another randomized comparison, cryosurgery plus triamcinolone produced greater height and volume reductions than CO_2 laser plus triamcinolone.[21] Shaving followed by contact cryosurgery achieved at least 50% volume reduction in 71% of scars, with 20% recurrence at 12 months.[21,22]

These findings suggest that cryotherapy is most useful as an adjunct to corticosteroid injection or surgical debulking rather than as monotherapy. Pain, atrophy, and hypopigmentation remain important limitations, particularly in darker skin phototypes, and outcomes appear most favorable in younger, smaller lesions.[20,22]

CONCLUSION

Liquid nitrogen cryotherapy is more versatile than conventional indications suggest. Its effects vary with treatment intensity: ablative freezing produces direct cryonecrosis and vascular compromise, whereas superficial treatment may influence microcirculation, sensory signaling, and local immune activity. These mechanisms help explain its use across otherwise distinct conditions, from debulking Kaposi sarcoma and remodeling keloids to promoting hair regrowth in alopecia areata.

The strength of evidence, however, varies considerably by indication. The evidence is strongest for its use in local treatment for limited cutaneous KS and as an adjunct in keloids and LSC, while evidence for AA, PN, and GA remains limited by small or uncontrolled studies. Its affordability, portability, and repeatability may make it particularly useful when laser, surgery, injections, or systemic therapy are unavailable or poorly tolerated. Procedural pain, blistering, delayed healing, and pigmentary alteration remain important constraints, especially in patients with darker skin phototypes. Future studies should aim to standardize treatment protocols and evaluate durability, comparative efficacy, and patient selection.

DISCLOSURES

AZ's work is funded through an independent research grant from Galderma. AK's work is funded through independent research grants from Incyte and Johnson & Johnson. AK, AZ, CC, and AF have no conflicts to disclose.

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