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Topical Therapies for Pruritus

Sarina B. Elmariah, MD, PhD, and Ethan A. Lerner, MD, PhD

Itch, or pruritus, is the predominant symptom associated with acute and chronic cutaneous disease, and in some cases may be debilitating. To date, there is no single universally effective anti-itch treatment. Because the pathophysiology of itch in most cutaneous or systemic disorders remains unclear, antipruritic therapy is often directed against a variety of targets, including the epidermal barrier, immune system, or the nervous system. Topical therapy is the mainstay of dermatologic management of acute or localized itch or in patients with contraindications to systemic therapies. This review will summarize current topical therapies to treat pruritus and discuss potential future therapies.
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Itch, also known as pruritus, is defined as an unpleasant sensation evoking the desire to scratch. Despite being the major symptom associated with skin disease, our understanding of the pathogenesis of most types of itch is limited, and current therapies are often inadequate. Moreover, although the treatment of acute itch is usually straightforward, management of chronic itch frequently poses a therapeutic dilemma for many clinicians. Topical therapy remains the cornerstone in managing acute or localized itch, or more widespread dermatoses in patients in whom systemic therapy is less desirable because of polypharmacy, disease co-moribities, or other contraindications. Depending on the clinical scenario, patients may benefit from judicious use of different topical formulations that are directed at different cutaneous, immune, or neural targets. This review will summarize current topical therapies to treat itch and discuss emerging antipruritic therapies based on our growing understanding of itch pathophysiology.

Moisturizers, Emollients, and Barrier Protection

Moisturizers have long been used to maintain the integrity of the epidermal barrier and promote its protective function against dehydration, irritants, allergens, and infectious pathogens, all of which may precipitate itch and/or pain. Increases in transepidermal water loss, which suggest decreased barrier function, are associated with increased intensity of pruritus in atopic dermatitis (AD) and other itchy dermatoses (Table 1).[1] Disturbances in the cornified layer in particular may be attributable to the loss of specific structural proteins, poor hydration, or may be multifactorial and lend to altered barrier protection.

Moisturizing is aimed at replenishing the cornified layer to restore normal barrier function, in part by rehydrating or "plumping" the corneocytes and by restoring the structure of the lipid bilayer of corneocytes within the lower stratum corneum. All commercially available moisturizer formulations contain a combination of humectants (which attract and hold water in the skin, e. g., glycerol, lactate, urea), occlusives (which prevent evaporation, e. g., petrolatum, mineral oil), and emollients (oils or lipids that provide partial hydration and occlusion, e. g., sterols, lanolin, glycol and glyceryl stearates).[2] In general, moisturizers should be applied one to three times daily to xerotic skin and especially within minutes of bathing for optimal occlusion of a hydrated stratum corneum.[3]

No particular moisturizer formulation has consistently proven superior to others for improving skin barrier function. In general, ointments or thick creams containing high lipid content are preferred over lotions or gels. Glycerol-based moisturizers have been shown to increase stratum corneum hydration and thickness and can alleviate inflammation and itch in atopic skin.[1,4] Several nonsteroidal barrier creams, recently introduced on the market as "medical devices" for the treatment of AD, are thought to incorporate directly into the structural framework of the skin and are safe and effective in treating atopic pediatric and adult patients.[5-7]

Department of Dermatology, Massachusetts General Hospital, Boston, MA.
Dr Elmariah is an Instructor at Harvard Medical School and Graduate Assistant in Dermatology at MGH.
Dr Lerner is an Associate Professor of Dermatology at Harvard Medical School.
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Address reprint requests to Ethan A. Lerner, MD, PhD, Department of Dermatology, Cutaneous Biology Research Center, Bldg 149, 13th Street, Charlestown, MA 02129. E-mail: elerner@partners.org

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Table 1 Topical Barrier and Immunomodulatory Antipruritic Therapies

Therapy	Mechanism of Action	Pruritic Disorders With Reported Benefit	Comments
Moisturizers	Barrier reinforcement and repair	Xerosis, atopic dermatitis (AD), allergic contact dermatitis (ACD), psoriasis	May be recommended for general use
Glycerol, lactate(s), urea, sorbital	Humectant		
Petrolatum, mineral oil, dimethicone	Occlusive		
Glycol stearate, glyceryl stearate, lanolin	Emollient		
Repair creams	Lipid and ceramide incorporation into corneocyte scaffold		
Corticosteroids	Activates glucocorticoid receptors that inhibit proinflammatory cytokine release	AD, ACD, psoriasis, prurigo nodularis (PN), lichen simplex chronicus (LSC)	Limit duration and site application of ultra or highly potent topical steroids Low to very low potency steroids preferred for face and intertriginous areas
Calcineurin inhibitors	Prevents activation of the nuclear factor of activated T cells transcription factor in T cells which inhibits T cell activation and pro-inflammatory cytokine release	AD, PN, hand dermatitis, rosacea, lichen sclerosis, anogenital pruritus	Burning sensation with initial use may limit patient compliance
Vitamin D analogues	Inhibits tumor necrosis factor-α expression, keratinocyte proliferation and differentiation	Psoriasis, PN, polymorphous light eruption	
Antihistamines	Blocks histamine 1 and/or 2 receptors on histamine-sensitive sensory fibers	AD, ACD, LSC, nummular dermatitis	Trials testing efficacy of topical formulations are inconclusive, except for topical doxepin May cause sedation with systemic absorption

These formulations contain various combinations of lipids, such as triglycerides and free fatty acids, cholesterol, phospholipids, ceramides, squalene, and phytosterol, all of which are thought to reinforce the cornified layer scaffold. Barrier cream preparations may also contain hyaluronic acid or various humectants to hydrate corneocytes, as well as antiinflammatory agents, such as glycyrrhetinic acid, *N*-palmitoylthanolamine, and antioxidants. Although more comparative clinical trials are needed, several investigators suggest that pure petrolatum and lipid-containing creams are equally effective in repairing the skin barrier after experimental perturbation and in the setting of chronic dermatitis.[8,9] Emollients rich in ceramides have also been shown to be effective in blocking transepidermal water loss and improving clinical disease scores.[10]

In addition to hydration and structurally barrier reinforcement, emerging agents may accelerate recovery from barrier damage via yet-unknown mechanisms. Application of capesazepine, a transient receptor potential vanilloid type 1 (TRPV1) antagonist, accelerates recovery from barrier damage in humans and can attenuate dermatitis-associated barrier damage in mouse models.[11,12] Similarly, a newly developed prostanoid (ie, DP1) receptor agonist known as TS-022 can significantly accelerate the repair of the cutaneous barrier disruption caused by mechanical scratching.[13] The exact mechanism by which these agents act to improve barrier repair is unknown, but such agents may soon be incorporated into moisturizers and may prove helpful in preventing exacerbations in various pruritic skin disorders.

Topical Corticosteroids

Topical corticosteroids (Table 2) are first-line therapy for acute pruritus associated with moderate-to-severe inflammatory skin diseases, such as AD, allergic contact dermatitis,

Table 2 Topical Corticosteroid Formulations

Potency Class	Corticosteroid	Available Formulations
I (ultra high)	Clobetasol propionate 0.05%	Cream, ointment
	Halobetasol proprionate 0.05%	Cream, ointment
	Augmented betamethasone dipropionate 0.05%	Gel, ointment
	Fluocinonide 0.1%	Cream
	Diflorasone diacetate 0.05%	Ointment
II (high)	Betamethasone dipropionate 0.05%	Ointment
	Augmented betamethasone dipropionate 0.05%	Lotion, cream
	Desoximetasone 0.25%	Cream, ointment
	Amcinonide 0.1%	Ointment
	Desoximetasone 0.05-0.25%	Gel, cream, ointment
	Diflorasone diacetate 0.05%	Cream
	Fluocinonide 0.05%	Solution, gel, cream, ointment
III (medium)	Betamethasone dipropionate 0.05%	Cream
	Betamethasone valerate 0.1%	Ointment
	Amcinonide 0.1%	Cream
	Fluticasone propionate 0.005%	Ointment
	Triamcinolone diacetate 0.5%	Cream, ointment
IV (medium)	Hydrocortisone valerate 0.2%	Ointment
	Mometasone furoate 0.1%	Lotion, cream, ointment
	Triamcinolone acetonide 0.1%	Ointment
V (medium)	Betamethasone valerate 0.1%	Cream
	Fluticasone propionate 0.05	Cream
	Hydrocortisone butyrate 0.1%	Solution, cream, ointment
	Hydrocortisone valerate 0.2%	Cream
	Triamcinolone acetonide 0.025-0.1%	Cream
VI (low)	Alclometasone dipropionate 0.05%	Cream, ointment
	Desonide 0.05%	Cream
	Fluocinolone acetonide 0.01%	Solution, cream
VII (very low)	Hydrocortisone 0.5-2.5%	Lotion, cream, ointment

psoriasis, and lichen planus. Although the exact mechanism of action is not known, topical corticosteroids are thought to activate glucocorticoid receptors that inhibit cytokine activation, thereby decreasing local inflammation and indirectly controlling pruritus. Thus, although frequently used by health practitioners to treat patients with pruritus of unknown etiology, it must be emphasized that topical corticosteroids are of limited to no benefit in patients with noninflammatory itch.

There are more than 30 different topical steroid formulations available in the United States, and these are prepared in different bases (eg, solution, lotion, cream or ointment). Topical corticosteroids range in potency from low (class VII) to high or ultrapotent (class I). It is generally accepted that the clinical efficacy to treat inflammation, and indirectly pruritus, correlates with steroid potency.

Optimal use of topical corticosteroids usually involves the use of medium to ultrapotent formulations on a daily to twice-daily basis for short courses lasting one to three weeks to pruritic areas or dermatitis on the trunk or extremities and lower-potency agents on the face or intertriginous areas. One study demonstrated that twice-daily application of fluocinonide 0.1% cream for three days was well tolerated by atopic patients and resulted in a 79% decrease in pruritus from baseline using the pruritus visual analog scale.[14] A small pilot study in patients with pruritus from undefined etiologies demonstrated that topical application of hydrocortisone acetate 2.5% and pramoxine hydrochloride 1% in a hydrolipid lotion reduced pruritus by 30% from baseline as rated by patients using the visual analog scale within 24 hours of initiation of therapy.[15]

In various clinical scenarios, prolonged use of medium to ultrapotent topical steroids with close clinical monitoring may be indicated. A randomized, double-blind study demonstrated that twice-weekly application of fluticasone proprionate, a medium potency steroid, in both cream and ointment forms, was sufficient to control relapses of rash and pruritus in atopic patients during a 16-week duration.[16] Ultrapotent topical steroids, such as betamethasone dipropionate, are often used as first-line agents in prurigo nodularis, and when combined with occlusive bandages, are thought to be particularly useful to interrupt the itch–scratch cycle.[17] Similarly, prolonged but localized application of potent topical steroids has been helpful at controlling pruritus associated with dermatoses affecting mucosal sites. For example, a double-blind, randomized trial comparing the effects of clobetasol 0.05% cream with pimecrolimus 1% cream in patients with vulvar lichen sclerosus showed a significant decrease in inflammation, pruritus, and burning with use of clobetasol once daily during a 12-week treatment period, and this was shown to be superior overall to pimecrolimus.[18]

The use of topical steroids should be limited and potentially avoided in cases of generalized cutaneous disease or prolonged daily treatment duration because of the risk of local side effects, including atrophy, striae, pigment alteration, acne, petechiae, telangiectasia, and the potential risk from systemic absorption, including hypothalamus-pituitary axis suppression. Although tachyphylaxis, defined as a decreasing response after administration of a few doses, has been demonstrated with use of topical steroids in several experimental settings, the clinical significance of this in pruritic disorders, such as AD and psoriasis is unclear.[19,20]

Topical Calcineurin Inhibitors

Topical calcineurin inhibitors (TCIs), such as tacrolimus and pimecrolimus, are immunomodulators that have been shown to be effective in reducing pruritus in patients with AD, chronic irritant hand dermatitis, rosacea, lichen sclerosis, anogenital pruritus, and prurigo nodularis.[21,22] The underlying mechanisms of the ability of TCIs to reduce pruritus are unclear and may be multifactorial. TCIs regulate T-cell activation and inhibit release of various inflammatory cytokines.[23,24] Although initially thought to act solely via their antiinflammatory properties, TCIs may also mediate their antipruritic effects by activating and then desensitizing TRPV1 located on peripheral nerve fibers.[25,26]

Treatment with TCIs has been effective at reducing pruritus within 48 hours of initial application, and its antipruritic effects are maintained during prolonged use.[22] In multiple large double-blind, randomized, vehicle-controlled trials in pediatric patients, tacrolimus ointment was shown to offer rapid relief from pruritus and other the symptoms of AD, with significant improvement observed within the first week of treatment.[27-29] Similarly, in a randomized, double-blind, vehicle-controlled trial of pimecrolimus cream in atopic pediatric patients, 44.2% of pimecrolimus-treated patients versus 25.7% of those on vehicle reported a reduction in pruritus from moderate/severe to absent/mild within one week of twice daily application and the antipruritic effect persisted during a six-week treatment course.[30] An extension phase of this study demonstrated continued control of AD lesions and pruritus during an additional 20-week period of open-label use.[31] In several active-comparator studies, researchers have shown that tacrolimus ointment is more efficacious than pimecrolimus cream in the treatment of AD symptoms, including pruritus, while sharing a similar safety profile.[32,33] Although TCIs are well-tolerated and superior to vehicle alone in preventing relapse of AD, a recent meta-analysis suggested that topical tacrolimus may not be as efficacious as topical fluticasone propionate to prevent flares of AD and pruritus.[34-36]

Common side effects of TCIs are transient burning and stinging sensations, which may in part be attributable to their activation of TRPV1 on peripheral nerves.[30] Unlike topical corticosteroids, TCIs do not cause skin atrophy with prolonged use and are considered safe for use on facial, genital, and intertriginous skin. Moreover, studies on chronic use of TCIs in AD patients have revealed no significant risk of systemic immunosuppression or increase in rate of serious infections.[33] In addition, although TCIs are only approved for use in adults and children >2 years old, retrospective studies of patients younger than two years with moderate-to-severe AD have demonstrated that use of tacrolimus ointment (0.1% or 0.03%) improved symptoms of AD with minimal systemic absorption and no significant adverse effects.[37]

Despite the Blackbox warning issued by the Food and Drug Administration in 2006 based on studies in animals and transplant patients, no prospective clinical studies demonstrate an overall increase in the risk of cancer in pediatric or adult atopic populations following use of TCIs.[33,38] One retrospective cohort study found that the hazard ratio for T-cell lymphoma was 5.44 for users of topical tacrolimus, and slightly, but not significantly, elevated for users of pimecrolimus.[39] There was no statistically significant increase in the risk for nonmelanoma or melanoma skin cancers.[39] Ongoing longitudinal observational studies are being conducted to address the risk of lymphoma and long-term safety concerns with use of TCIs.

Topical Vitamin D Modulators

Topical vitamin D3 or its analogues, such as calcipotriol that has been used widely for the treatment of psoriasis, may also be useful to treat pruritus in some clinical scenarios. Vitamin D3 down-regulates cellular adhesion molecule expression by inhibiting tumor necrosis factor-α mRNA expression and influences keratinocyte proliferation and differentiation. In two randomized, double-blind clinical trials, twice-daily application of calcitriol ointment for eight weeks resulted in significant improvements in pruritus compared with vehicle ointment, in addition to reducing other symptoms of psoriasis.[40] Topical vitamin D3 has also been reported to be effective in treating the intensely pruritic lesions of prurigo nodularis.[41] A double-blind, right/left comparison of calcipotriol 50 mg g^{-1} ointment and betamethasone valerate 0.1% ointment in the treatment of prurigo nodularis demonstrated that calcipotriol was more effective in reducing the size and number of prurigo nodules.[42] Vitamin D3 has been shown to reduce the number of epidermal FcR1+ dendritic cells in prurigo lesions; however, the significance of this finding to understand its antipruritic effects remains unclear. Finally, a randomized, double-blind right/left comparison study of calcipotriol and placebo creams in patients with polymorphous light eruption showed that twice daily application of calcipotriol for seven days before ultraviolet irradiation significantly decreased pruritus compared with placebo.[43]

Topical vitamin D3 analogues have been shown to be safe and well-tolerated in several short-term and long-term clinical trials. Pharmacokinetic studies in both healthy and psoriasis patients have demonstrated that topical calcitriol ointment produces little systemic absorption and does not alter systemic calcium or phosphorous metabolism significantly even when applied to approximately one-third of the body surface area.[44]

Topical Antihistamines

Topical antihistamines, although widely used to treat itch and available without a prescription, offer limited benefit in the treatment of pruritic conditions. In general, studies on topical antihistamines, including topical diphenhydramine, have been inconsistent, inconclusive or limited in design (small patient number, no placebo group, nonrandomized).[45] Only topical doxepin, a tricyclic antidepressant and potent H1 and H2 antagonist, has been shown to significantly reduce pruritus in patients with AD, lichen simplex chronicus, contact dermatitis and nummular dermatitis.[46,47] However, topical doxepin may cause localized burning, allergic contact dermatitis, and has been reported to cause drowsiness because of systemic absorption in up to 25% of patients.[46,47] Thus, despite its potential benefit, use of topical doxepin is limited by its side effect profile and it is best avoided in children and used with caution in elderly patients.

Topical Neuromodulators

Topical anesthetics (Table 3), such as lidocaine 5% or the eutectic mixture of lidocaine 2.5%−prilocaine 2.5%, pramoxine 1%, and polidocanol 3%, have all been shown to have antipruritic effects and have been used successfully in several pruritic conditions.[48] Lidocaine and prilocaine are both aminoamide anesthetics which inhibit sodium flux through voltage-gated sodium channels and thereby stabilize sensory fibers and block itch and pain sensation. Topical lidocaine alone or as a eutectic mixture with Prilocaine has been used to effectively treat pruritus in patients with notalgia paresthetica, pruritus ani, and postburn pruritus.[49-51] Potential side effects of "Caine" anesthetics include paresthesias, allergic contact dermatitis (usually because of metabolites of aminoester formulations), and methemoglobinemia necessitating avoidance in infant and pregnant patients.[52]

Pramoxine, which is thought to exert antipruritic effects by stabilizing membranes of sensory nerves, effectively decreases itch in patients with xerosis, uremic pruritus, and psoriasis and has been used as a single agent or in combina-

Table 3 Topical Neuromodulatory Antipruritic Therapies

Therapy	Mechanism of Action	Pruritic Disorders Wth Reported Benefit	Comments
Topical anesthetics			
Lidocaine, 2.5-5%	Blocks voltage gated Na channels	Neuropathic pruritus	
Prilocaine, 2.5%		Pruritus ani, postburn pruritus, prurigo nodularis (PN)	Prilocaine associated with methemoglobinemia in pediatric patients
Pramoxine, 1%	Stabilizes neuronal membrane by uncertain mechanism	Xerosis, uremic pruritus (UP), psoriasis	
Polidocanol 3%	Non-ionic surfactant	atopic dermatitis (AD), contact dermatitis, psoriasis, idiopathic pruritus	Formulated with urea
Capsaicin	Activates TRPV1 on sensory fibers, depleting substance P over time and prevents neural transmission	AD, UP, brachioradial pruritus, pruritus ani, PN, aquagenic pruritus	Burning sensation with initial use may limit patient compliance
Menthol	Activates TRPM8 on sensory fibers triggering a cooling sensation	Lichen amyloidosis, as well as hydroxyethyl starch-induced, histamine-induced, and mustard gas-induced pruritus	May be useful in patients who report cooling alleviates symptoms
N-palmitoylethanolamine cream	Cannabinoid receptor CB2 agonist	AD, PN, lichen simplex chronicus, UP	Efficacy demonstrated in pilot studies only Not Food and Drug Administration (FDA) approved for itch
Naltrexone, 1% cream	μ-opioid receptor antagonist	AD	Not FDA approved for itch
Aprepitant	Neurokinin 1 receptor antagonist	PN, nephrogenic pruritus, Sézary syndrome, paraneoplastic and drug-induced pruritus	Efficacy demonstrated in pilot studies only Not FDA approved for itch

tion with mild potency topical steroids or lactic acid lotion.[15,53-55] In a randomized, double-blind, comparative trial in patients suffering from uremic pruritus, twice daily application of pramoxine, 1% lotion for four weeks significantly reduced pruritus compared to a control lotion and was generally well-tolerated.[54]

Polidocanol is a non-ionic surfactant with both local anesthetic properties and moisturizing effects. In an open-label, multicenter, drug monitoring survey of 1611 pediatric and adult patients, a combination of 5% urea and 3% polidocanol was found to significantly reduce or completely alleviate pruritus in 50% of patients with AD, contact dermatitis, psoriasis or idiopathic pruritus.[56] Antipruritic effects were evident in 25% of patients as early as two weeks, the first time point of evaluation, and the mixture was well-tolerated with only 2.8% of cases reporting adverse events, including mild burning or itching.[56]

Topical capsaicin, which activates TRPV1 on cutaneous sensory nerves triggering release and then depletion of neuropeptides, such as substance P, and thereby limiting neural transmission from these fibers over time, has been used to treat itching in various pruritic disorders. Numerous reports and clinical studies have described successful treatment of symptoms in patients with notalgia paresthetica, brachioradial pruritus, pruritus ani, prurigo nodularis, aquagenic pruritus, and uremic pruritus.[57-62] In one study of 33 patients with prurigo nodularis, application of topical capsaicin four to six times daily demonstrated complete remission of itch in all patients within two weeks.[61] Control of pruritus with topical capsaicin lasted for up to as long as 10 months with continued use, but recurred soon after treatment discontinuation.[61] However, a recent systematic review of existing controlled trials to test the efficacy of capsaicin as an antipruritic found numerous methodological concerns with these trials and concluded that there is no convincing evidence for the use of capsaicin to treat pruritus in any medical condition.[63] A common side effect of topical capsaicin is a transient burning sensation and local erythema with initial application. Patients should be warned about this effect and may benefit from simultaneous application of a topical anesthetic for the first few days of use to improve overall compliance. Limited hyperalgesia and neurogenic inflammation has been reported in African American patients in response to topical capsaicin.[64]

Topical menthol, a monoterpene isolated from the essential oils of *Menthe piperita* and *Mentha arvesis*, has been used since ancient times for its antipruritic and analgesic effects.[65] Menthol elicits a cool sensation via activation of TRPM8, a temperature-sensitive member of the melastatin transient receptor potential subfamily expressed on cutaneous sensory fibers.[66] The antipruritic effect of menthol has been described for lichen amyloidosis, as well as hydroxyethyl starch-induced, histamine-induced, and mustard gas-induced pruritus.[65,67-69] Of note, menthol at concentrations of 1%-3% have been reported to relieve pruritus, whereas greater dose preparations, such as 10% solutions can induce irritation.[48,65]

Future Therapies

As our understanding of the immune and neural pathophysiology of itch evolves, novel antipruritic therapies are emerging that may prove helpful in the treatment of both acute and chronic itch. Several topical and systemic agents that target receptors on the unmyelinated, polymodal C-fibers that initiate the sensation of itch in the periphery or on the spinal and supraspinal neuronal circuits that further relay this sensation have already shown promise in the treatment of different pruritic conditions.

Cannabinoid receptors, CB1 and CB2, are expressed on cutaneous sensory nerve fibers, mast cells and keratinocytes.[70] When administered topically to patients via patch delivery, a cannabinoid receptor agonist reduced the severity of histamine-induced itch in humans. This effect was thought to be due to decreased neurogenic stimulation as opposed to decreased histaminergic activity because histamine-induced protein extravasation was still elevated in the skin as measured by microdialysis.[71] *N*-palmitoylethanolamine, a cannabinoid receptor CB2 agonist, has been compounded into creams and shown to reduce pruritus within days in patients with AD, lichen simplex chronicus, prurigo nodularis, and uremic pruritus.[72-74] Thus far, compounds with *N*-palmitoylethanolamine have been tolerated well with few to no side effects.[74]

With the growing observation that members of the opioid receptor family modulate both pain and itch, opioid signaling has become a recent target for antipruritic therapy.[75,76] In a pilot study of 18 patients with different chronic pruritic disorders, more than 70% of the patients using the μ-opioid receptor antagonist naltrexone in a topical 1% cream experienced a significant reduction of pruritus.[75] A subsequent, randomized, placebo-controlled, crossover trial was performed with the same formulation in 40 patients with AD and demonstrated that naltrexone had an overall 29.4% better effect compared with placebo, with the ability to reduce itch to 50% within 46 minutes.[75] Butorphanol, a combined μ-receptor antagonist and κ-receptor agonist that has shown considerable promise in the management of intractable pruritus, is currently administered as a nasal spray and is not available in a topical formulation.[77]

Future antipruritic strategies may target other receptor families expressed in the skin and peripheral nervous system, including TRP family members as previously discussed, protease-activated receptor 2 (PAR2), neurokinin-1 receptors (NKR1), or interleukin-31 receptors. PAR2 is expressed by sensory nerve fibers in the skin and can be activated by mast cell mediators, such as tryptase or other endogenous or exogenous proteases.[10,78-80] Activation of PAR2 elicits pruritus and scratching in animal models, and PAR2 expression appears up-regulated in afferent nerve fibers in lesional skin from patients with AD.[78,81] Thus, PAR-2 antagonists may be a reasonable target to suppress peripherally induced pruritus. Neurokinin-1 receptors are expressed by neurons in the dorsal horn, as well as by multiple cell populations within the skin, including keratinocytes, endothelial cells and mast cells.[82,83] In response to binding substance P, NKR1 stimu-

lates elaboration of proinflammatory cytokines in the skin and stimulates neural transmission of itch. A small pilot study recently demonstrated that treatment with the NKR1 antagonist aprepitant decreased pruritus in patients with prurigo nodularis, nephrogenic pruritus, Sézary syndrome, paraneoplastic and drug-induced pruritus.[82] Finally, interest in targeting interleukin-31 signaling has grown in recent years because of observations that elevations in interleukin-31 are associated with severe pruritus and AD lesions in mice and humans.[84,85] Because interleukin-31 receptors are expressed by primary sensory afferent neurons and keratinocytes in the skin, these may pose a reasonable target for novel topical antipruritic therapies.[86,87]

Conclusions

Chronic itch arising in the setting of primary cutaneous or systemic disease may be severe and incapacitating. Choosing the appropriate therapy must reflect an understanding of the pathogenesis of a given disease and must be individualized and optimized for a given patient. Although many of the topical antipruritic preparations have been shown to be effective within the highly regimented and monitored framework of the aforementioned clinical studies or trials, the practical use of these agents by individual patients may vary dramatically. To optimize patient compliance and therefore improvement in their symptoms, it is critical that patients have a realistic expectation of the timeline of therapy and potential side effects. This expectation is crucial with respect to topical agents with direct neuromodulatory effects, such as capsaicin, tacrolimus, greater concentrations of menthol, and others, because these can initially induce a burning sensation that frequently precipitates discontinuation. Although topical therapies are the cornerstone of antipruritic treatment, combining such therapies with systemic anti-itch agents may prove beneficial for more challenging cases involving generalized pruritus or pruritus because of systemic disease. Our armamentarium of antipruritic agents is growing, however more thorough investigation of older, established and newer emerging therapies must be performed, with an emphasis on double-blind, randomized, placebo-controlled or active comparator trials.

References

1. Lee CH, Chuang HY, Shih CC, et al: Transepidermal water loss, serum IgE and beta-endorphin as important and independent biological markers for development of itch intensity in atopic dermatitis. Br J Dermatol 154:1100-1107, 2006
2. Rawlings AV, Canestrari DA, Dobkowski B: Moisturizer technology versus clinical performance. Dermatol Ther 17 Suppl 1:49-56, 2004
3. Simpson EL: Atopic dermatitis: A review of topical treatment options. Curr Med Res Opin 26:633-640, 2010
4. Breternitz M, Kowatzki D, Langenauer M, et al: Placebo-controlled, double-blind, randomized, prospective study of a glycerol-based emollient on eczematous skin in atopic dermatitis: Biophysical and clinical evaluation. Skin Pharmacol Physiol 21:39-45, 2008
5. Patrizi A, Capitanio B, Neri I, et al: A double-blind, randomized, vehicle-controlled clinical study to evaluate the efficacy and safety of MAS063DP (ATOPICLAIR) in the management of atopic dermatitis in paediatric patients. Pediatr Allergy Immunol 19:619-625, 2008
6. Abramovits W, Boguniewicz M: A multicenter, randomized, vehicle-controlled clinical study to examine the efficacy and safety of MAS063DP (Atopiclair) in the management of mild to moderate atopic dermatitis in adults. J Drugs Dermatol 5:236-244, 2006
7. Bikowski J: Case studies assessing a new skin barrier repair cream for the treatment of atopic dermatitis. J Drugs Dermatol 8:1037-1041, 2009
8. Kucharekova M, Van De Kerkhof PC, Van Der Valk PG: A randomized comparison of an emollient containing skin-related lipids with a petrolatum-based emollient as adjunct in the treatment of chronic hand dermatitis. Contact Dermatitis 48:293-299, 2003
9. Lodén M, Bárány E: Skin-identical lipids versus petrolatum in the treatment of tape-stripped and detergent-perturbed human skin. Acta Derm Venereol 80:412-415, 2000
10. Chamlin SL, Kao J, Frieden IJ, et al: Ceramide-dominant barrier repair lipids alleviate childhood atopic dermatitis: Changes in barrier function provide a sensitive indicator of disease activity. J Am Acad Dermatol 47:198-208, 2002
11. Yun JW, Seo JA, Jeong YS, et al: TRPV1 antagonist can suppress the atopic dermatitis-like symptoms by accelerating skin barrier recovery. J Dermatol Sci 62:8-15, 2011
12. Denda M, Sokabe T, Fukumi-Tominaga T, et al: Effects of skin surface temperature on epidermal permeability barrier homeostasis. J Invest Dermatol 127:654-659, 2007
13. Arai I, Takaoka A, Hashimoto Y, et al: Effects of TS-022, a newly developed prostanoid DP1 receptor agonist, on experimental pruritus, cutaneous barrier disruptions and atopic dermatitis in mice. Eur J Pharmacol 556:207-214, 2007
14. Yentzer BA, Ade RA, Fountain JM, et al: Improvement in treatment adherence with a 3-day course of fluocinonide cream 0.1% for atopic dermatitis. Cutis 86:208-213, 2010
15. Kircik LH: Efficacy and onset of action of hydrocortisone acetate 2.5% and pramoxine hydrochloride 1% lotion for the management of pruritus: Results of a pilot study. J Clin Aesthet Dermatol 4:48-50, 2011
16. Berth-Jones J, Damstra RJ, Golsch S, et al: Twice weekly fluticasone propionate added to emollient maintenance treatment to reduce risk of relapse in atopic dermatitis: Randomised, double blind, parallel group study. BMJ 326:1367, 2003
17. Lee MR, Shumack S: Prurigo nodularis: A review. Australas J Dermatol 46:211-218, 2005; quiz: 9-20
18. Goldstein AT, Creasey A, Pfau R, et al: A double-blind, randomized controlled trial of clobetasol versus pimecrolimus in patients with vulvar lichen sclerosus. J Am Acad Dermatol, in press
19. Miller JJ, Roling D, Margolis D, et al: Failure to demonstrate therapeutic tachyphylaxis to topically applied steroids in patients with psoriasis. J Am Acad Dermatol 41:546-549, 1999
20. Singh S, Gupta A, Pandey SS, et al: Tachyphylaxis to histamine-induced wheal suppression by topical 0.05% clobetasol propionate in normal versus Croton oil-induced dermatitic skin. Dermatology (Basel) 193: 121-123, 1996
21. Stander S, Schurmeyer-Horst F, Luger TA, et al: Treatment of pruritic diseases with topical calcineurin inhibitors. Ther Clin Risk Manag 2:213-218, 2006
22. Kaufmann R, Bieber T, Helgesen AL, et al: Onset of pruritus relief with pimecrolimus cream 1% in adult patients with atopic dermatitis: A randomized trial. Allergy 61:375-381, 2006
23. Grassberger M, Baumruker T, Enz A, et al: A novel anti-inflammatory drug, SDZ ASM 981, for the treatment of skin diseases: In vitro pharmacology. Br J Dermatol 141:264-273, 1999
24. Kalthoff FS, Chung J, Stuetz A: Pimecrolimus inhibits up-regulation of OX40 and synthesis of inflammatory cytokines upon secondary T cell activation by allogeneic dendritic cells. Clin Exp Immunol 130:85-92, 2002
25. Senba E, Katanosaka K, Yajima H, et al: The immunosuppressant FK506 activates capsaicin- and bradykinin-sensitive DRG neurons and cutaneous C-fibers. Neurosci Res 50:257-262, 2004
26. Pereira U, Boulais N, Lebonvallet N, et al: Mechanisms of the sensory effects of tacrolimus on the skin. Br J Dermatol 163:70-77, 2010
27. Boguniewicz M, Fiedler VC, Raimer S, et al: A randomized, vehicle-controlled trial of tacrolimus ointment for treatment of atopic derma-

titis in children. Pediatric Tacrolimus Study Group. J Allergy Clin Immunol 102:637-644, 1998
28. Paller A, Eichenfield LF, Leung DY, et al: A 12-week study of tacrolimus ointment for the treatment of atopic dermatitis in pediatric patients. J Am Acad Dermatol 44:S47-S57, 2001
29. Schachner LA, Lamerson C, Sheehan MP, et al: Tacrolimus ointment 0.03% is safe and effective for the treatment of mild to moderate atopic dermatitis in pediatric patients: Results from a randomized, double-blind, vehicle-controlled study. Pediatrics 116:e334-e342, 2005
30. Eichenfield LF, Lucky AW, Boguniewicz M, et al: Safety and efficacy of pimecrolimus (ASM 981) cream 1% in the treatment of mild and moderate atopic dermatitis in children and adolescents. J Am Acad Dermatol 46:495-504, 2002
31. Langley RG, Eichenfield LF, Lucky AW, et al: Sustained efficacy and safety of pimecrolimus cream 1% when used long-term (up to 26 weeks) to treat children with atopic dermatitis. Pediatr Dermatol 25:301-307, 2008
32. Paller AS, Lebwohl M, Fleischer AB Jr, et al: Tacrolimus ointment is more effective than pimecrolimus cream with a similar safety profile in the treatment of atopic dermatitis: Results from 3 randomized, comparative studies. J Am Acad Dermatol 52:810-822, 2005
33. McCollum AD, Paik A, Eichenfield LF: The safety and efficacy of tacrolimus ointment in pediatric patients with atopic dermatitis. Pediatr Dermatol 27:425-436, 2010
34. Breneman D, Fleischer AB Jr, Abramovits W, et al: Intermittent therapy for flare prevention and long-term disease control in stabilized atopic dermatitis: A randomized comparison of 3-times-weekly applications of tacrolimus ointment versus vehicle. J Am Acad Dermatol 58:990-999, 2008
35. Paller AS, Eichenfield LF, Kirsner RS, et al: Three times weekly tacrolimus ointment reduces relapse in stabilized atopic dermatitis: A new paradigm for use. Pediatrics 122:e1210-e1218, 2008
36. Schmitt J, von Kobyletzki L, Svensson A, et al: Efficacy and tolerability of proactive treatment with topical corticosteroids and calcineurin inhibitors for atopic eczema: Systematic review and meta-analysis of randomized controlled trials. Br J Dermatol 164:415-428, 2011
37. Patel RR, Vander Straten MR, Korman NJ: The safety and efficacy of tacrolimus therapy in patients younger than 2 years with atopic dermatitis. Arch Dermatol 139:1184-1186, 2003
38. Arellano FM, Wentworth CE, Arana A, et al: Risk of lymphoma following exposure to calcineurin inhibitors and topical steroids in patients with atopic dermatitis. J Invest Dermatol 127:808-816, 2007
39. Hui RL, Lide W, Chan J, et al: Association between exposure to topical tacrolimus or pimecrolimus and cancers. Ann Pharmacother 43:1956-1963, 2009
40. Kircik L: Efficacy and safety of topical calcitriol 3 microg/g ointment, a new topical therapy for chronic plaque psoriasis. J Drugs Dermatol 8:s9-16, 2009
41. Katayama I, Miyazaki Y, Nishioka K: Topical vitamin D3 (tacalcitol) for steroid-resistant prurigo. Br J Dermatol 135:237-240, 1996
42. Wong SS, Goh CL: Double-blind, right/left comparison of calcipotriol ointment and betamethasone ointment in the treatment of Prurigo nodularis. Arch Dermatol 136:807-808, 2000
43. Gruber-Wackernagel A, Bambach I, Legat FJ, et al: Randomized double-blinded placebo-controlled intra-individual trial on 1,25-(OH)2 vitamin D3 analogue in polymorphic light eruption. Br J Dermatol, in press
44. Lebwohl M, Ortonne JP, Andres P, et al: Calcitriol ointment 3 microg/g is safe and effective over 52 weeks for the treatment of mild to moderate plaque psoriasis. Cutis 83:205-212, 2009
45. Eschler DC, Klein PA: An evidence-based review of the efficacy of topical antihistamines in the relief of pruritus. J Drugs Dermatol 9:992-997, 2011
46. Drake LA, Fallon JD, Sober A: Relief of pruritus in patients with atopic dermatitis after treatment with topical doxepin cream. The Doxepin Study Group. J Am Acad Dermatol 31:613-616, 1994
47. Drake LA, Millikan LE: The antipruritic effect of 5% doxepin cream in patients with eczematous dermatitis. Doxepin Study Group. Arch Dermatol 131:1403-1408, 1995
48. Patel T, Yosipovitch G: Therapy of pruritus. Expert Opin Pharmacother 11:1673-1682, 2010
49. Layton AM, Cotterill JA: Notalgia paraesthetica—Report of three cases and their treatment. Clin Exp Dermatol 16:197-198, 1991
50. Allenby CF, Johnstone RS, Chatfield S, et al: PERINAL–a new no-touch spray to relieve the symptoms of pruritus ani. Int J Colorectal Dis 8:184-187, 1993
51. Kopecky EA, Jacobson S, Bch MB, et al: Safety and pharmacokinetics of EMLA in the treatment of postburn pruritus in pediatric patients: A pilot study. J Burn Care Rehabil 22:235-242, 2001
52. Guay J: Methemoglobinemia related to local anesthetics: A summary of 242 episodes. Anesth Analg 108:837-845, 2009
53. Grove G, Zerweck C: An evaluation of the moisturizing and anti-itch effects of a lactic acid and pramoxine hydrochloride cream. Cutis 73: 135-139, 2004
54. Young TA, Patel TS, Camacho F, et al: A pramoxine-based anti-itch lotion is more effective than a control lotion for the treatment of uremic pruritus in adult hemodialysis patients. J Dermatol Treat 20:76-81, 2009
55. Dawn A, Yosipovitch G: Treating itch in psoriasis. Dermatol Nurs 18: 227-233, 2006
56. Freitag G, Höppner T: Results of a postmarketing drug monitoring survey with a polidocanol-urea preparation for dry, itching skin. Curr Med Res Opin 13:529-537, 1997
57. Barry R, Rogers S: Brachioradial pruritus—An enigmatic entity. Clin Exp Dermatol 29:637-638, 2004
58. Knight TE, Solar HT: (Brachioradial) pruritus—Response to capsaicin cream. Int J Dermatol 33:206-209, 1994
59. Lysy J, Sistiery-Ittah M, Israelit Y, et al: Topical capsaicin—A novel and effective treatment for idiopathic intractable pruritus ani: A randomised, placebo controlled, crossover study. Gut 52:1323-1326, 2003
60. Makhlough A: Topical capsaicin therapy for uremic pruritus in patients on hemodialysis. Iran J Kidney Dis 4:137-140, 2010
61. Ständer S, Luger T, Metze D: Treatment of prurigo nodularis with topical capsaicin. J Am Acad Dermatol 44:471-478, 2001
62. Lotti T, Teofoli P, Tsampau D: Treatment of aquagenic pruritus with topical capsaicin cream. J Am Acad Dermatol 30:232-235, 1994
63. Gooding SM, Canter PH, Coelho HF, et al: Systematic review of topical capsaicin in the treatment of pruritus. Int J Dermatol 49:858-865, 2010
64. Wang H, Papoiu AD, Coghill RC, et al: Ethnic differences in pain, itch and thermal detection in response to topical capsaicin: African Americans display a notably limited hyperalgesia and neurogenic inflammation. Br J Dermatol 162:1023-1029, 2010
65. Frölich M, Enk A, Diepgen TL, et al: Successful treatment of therapy-resistant pruritus in lichen amyloidosis with menthol. Acta Derm Venereol 89:524-526, 2009
66. Peier AM, Moqrich A, Hergarden AC, et al: A TRP channel that senses cold stimuli and menthol. Cell 108:705-715, 2002
67. Haught JM, Jukic DM, English JC, 3rd: Hydroxyethyl starch-induced pruritus relieved by a combination of menthol and camphor. J Am Acad Dermatol 59:151-153, 2008
68. Panahi Y, Davoodi SM, Khalili H, et al: Phenol and menthol in the treatment of chronic skin lesions following mustard gas exposure. Singapore Med J 48:392-395, 2007
69. Bromm B, Scharein E, Darsow U, et al: Effects of menthol and cold on histamine-induced itch and skin reactions in man. Neurosci Lett 187:157-160, 1995
70. Ständer S, Schmelz M, Metze D, et al: Distribution of cannabinoid receptor 1 (CB1) and 2 (CB2) on sensory nerve fibers and adnexal structures in human skin. J Dermatol Sci 38:177-188, 2005
71. Dvorak M, Watkinson A, McGlone F, et al: Histamine induced responses are attenuated by a cannabinoid receptor agonist in human skin. Inflamm Res 52:238-245, 2003
72. Eberlein B, Eicke C, Reinhardt HW, et al: Adjuvant treatment of atopic eczema: Assessment of an emollient containing N-palmitoylethanolamine (ATOPA study). J Eur Acad Dermatol Venereol 22:73-82, 2008
73. Szepietowski JC, Szepietowski T, Reich A: Efficacy and tolerance of the cream containing structured physiological lipids with endocannabinoids in the treatment of uremic pruritus: A preliminary study. Acta Dermatovenerol Croat 13:97-103, 2005
74. Ständer S, Reinhardt HW, Luger TA: Topical cannabinoid agonists. An

effective new possibility for treating chronic pruritus [in German]. Hautarzt 57:801-807, 2006
75. Bigliardi PL, Stammer H, Jost G, et al: Treatment of pruritus with topically applied opiate receptor antagonist. J Am Acad Dermatol 56: 979-988, 2007
76. Friedman JD, Dello Buono FA: Opioid antagonists in the treatment of opioid-induced constipation and pruritus. Ann Pharmacother 35:85-91, 2001
77. Dawn AG, Yosipovitch G: Butorphanol for treatment of intractable pruritus. J Am Acad Dermatol 54:527-531, 2006
78. Steinhoff M, Neisius U, Ikoma A, et al: Proteinase-activated receptor-2 mediates itch: A novel pathway for pruritus in human skin. J Neurosci 23:6176-6180, 2003
79. Ui H, Andoh T, Lee JB, et al: Potent pruritogenic action of tryptase mediated by PAR-2 receptor and its involvement in anti-pruritic effect of nafamostat mesilate in mice. Eur J Pharmacol 530:172-178, 2006
80. Reddy VB, Iuga AO, Shimada SG, et al: Cowhage-evoked itch is mediated by a novel cysteine protease: A ligand of protease-activated receptors. J Neurosci 28:4331-4335, 2008
81. Shimada SG, Shimada KA, Collins JG: Scratching behavior in mice induced by the proteinase-activated receptor-2 agonist, SLIGRL-NH2. Eur J Pharmacol 530:281-283, 2006
82. Ständer S, Siepmann D, Herrgott I, et al: Targeting the neurokinin receptor 1 with aprepitant: A novel antipruritic strategy. PLoS ONE 5:e10968, 2010
83. Ständer S, Raap U, Weisshaar E, et al: Pathogenesis of pruritus. J Dtsch Dermatol Ges, in press
84. Takaoka A, Arai I, Sugimoto M, et al: Involvement of IL-31 on scratching behavior in NC/Nga mice with atopic-like dermatitis. Exp Dermatol 15:161-167, 2006
85. Raap U, Wichmann K, Bruder M, et al: Correlation of IL-31 serum levels with severity of atopic dermatitis. J Allergy Clin Immunol 122: 421-423, 2008
86. Heise R, Neis MM, Marquardt Y, et al: IL-31 receptor alpha expression in epidermal keratinocytes is modulated by cell differentiation and interferon gamma. J Invest Dermatol 129:240-243, 2009
87. Sonkoly E, Muller A, Lauerma AI, et al: IL-31: A new link between T cells and pruritus in atopic skin inflammation. J Allergy Clin Immunol 117:411-417, 2006