Topical Therapies for Pruritus

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Abstract

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. As the pathophysiology of itch in most cutaneous or systemic disorders remains unclear, anti-pruritic 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.

Keywords

itch; pruritus; topical therapy; barrier repair; corticosteroid; neuromodulator

Introduction

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, while 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 due to 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 anti-pruritic therapies based on our growing understanding of itch pathophysiology.

Moisturizers, emollients and barrier protection (Table 1)

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 (TEWL), which suggest decreased barrier function, are associated with increased intensity of pruritus in atopic dermatitis (AD) and other itchy dermatoses.[1] Disturbances in the cornified layer in particular may be due to 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 in order 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 once or 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] 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 anti-inflammatory agents such as glycyrrhetinic acid, N-palmitoylthanolamine and anti-oxidants. Although more comparative clinical trials are needed, several studies 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 TEWL 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 (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 (Table 2)

Topical corticosteroids are first line therapy for acute pruritus associated with moderate to severe inflammatory skin diseases, such as AD, allergic contact dermatitis, psoriasis and lichen planus. While 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, while frequently employed by health practicioners to treat patients with pruritus of unknown etiology, it must

be emphasized that topical corticosteroids are of limited to no benefit in patients with non-inflammatory itch.

There are over 30 different topical steroid formulations available in the United States and these are prepared in different bases (e.g. solution, lotion, cream or ointment). Topical corticosteroids range in potency from low (Class VII) to high or ultra-potent (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 using medium to ultra-potent formulations on a daily to twice daily basis for short courses lasting 1–3 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 3 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 ultra-potent 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 over a 16-week duration.[16] Ultra-potent 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 over 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 due to 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. While 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), 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 multi-factorial. TCIs regulate T-cell activation and inhibit release of various inflammatory cytokines.[23, 24] While initially thought to act solely via their anti-inflammatory properties, TCIs may also mediate their anti-pruritic effects by activating and then desensitizing TRPV1 located on peripheral nerve fibers. [25, 26]

Treatment with TCIs has been shown to be effective at reducing pruritus within 48 hours of initial application, and its anti-pruritic 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 1 week of twice daily application and the anti-pruritic effect persisted during a 6-week treatment course.[30] An extension phase of this study demonstrated continued control of AD lesions and pruritus over an additional 20-week period of open label use.[31] Several active-comparator studies 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] While 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 due 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 signficiant risk of systemic immunosuppresion or increase in rate of serious infections.[33] In addition, while TCIs are only approved for use in adults and children > 2 years old, retrospective studies of patients younger than 2 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 FDA 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 non-melanoma or melanoma skin cancers.[39] Ongoing longitudinal observational studies are being conducted to address the risk of lymphoma and longterm 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 downregulates cellular adhesion molecule expression by inhibiting TNF-α mRNA expression and influences keratinocyte proliferation and differentiation. In two randomized, double-blind clinical trials, twice-daily application of calcitriol ointment for 8 weeks resulted in significant improvements in pruritus compared to vehicle ointment, in addition to reducing other symptoms of psoriasis.[40] Topical vitamin D3 has also been reported to be effective in the treating the intensely pruritic lesions of prurigo nodularis.[41] A double-blind, right/left comparison of calcipotriol 50 mg/gm 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 understanding its anti-pruritic effects remain 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 7 days prior to UV irradiation significantly decreased pruritus compared to placebo.[43]

Topical vitamin D3 analogues have been shown to be safe and well-tolerated in a number of 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, while 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, non-randomized).[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 due to 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 the elderly.

Topical neuromodulators (Table 3)

Topical anesthetics 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 anti-pruritic effects and have been used successfully in a number of 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 parasthesias, allergic contact dermatitis (usually due to metabolites of aminoester formulations), and methemoglobinemia necessitating avoidance in infant and pregnant patients.[52]

Pramoxine, which is thought to exert anti-pruritic 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 combination 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 4 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, multi-center, 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] Anti-pruritic effects were evident in 25% of patients as early as 2 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 4 to 6 times daily demonstrated complete remission of itch in all patients within 2 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 anti-pruritic 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 *M. arvesis*, has been used since ancient times for its anti-pruritic 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 anti-pruritic 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 to 3% have been reported to relieve pruritus, while higher 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 anti-pruritic 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 attenuated histamine-induced itch in humans. This effect was thought to be due to decreased neurogenic stimulation as opposed to decreased histaminergic activity since 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 anti-pruritic 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 anti-pruritic 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 IL-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 upregulated 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 stimulates elaboration of pro-inflammatory 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 IL-31 signaling has grown in recent years due to observations that elevations in IL-31 are associated with severe pruritus and AD lesions in mice and humans.[84, 85] As IL-31 receptors are expressed by primary sensory afferent neurons and keratinocytes in the skin, these may pose a reasonable target for novel topical anti-pruritic 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. While many of the topical anti-pruritic preparations have been shown to be effective within the highly regimented and monitored framework of clinical studies or trials described above, 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 capsaicin, tacrolimus, higher concentrations of menthol and others, as these can initially induce a burning sensation which frequently precipitates discontinuation. While topical therapies are the cornerstone of anti-pruritic treatment, combining such therapies with systemic anti-itch agents may prove beneficial for more challenging cases involving generalized pruritus or pruritus due to systemic disease. Our armamentarium of anti-pruritic 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.

Acknowledgments

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Table 1

Topical barrier and immunomodulatory anti-pruritic 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 pro-inflammatory 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 NFAT transcription factor in T cells which inhibits T cell activation and proinflammatory cytokine release	AD, PN, hand dermatitis, rosacea, lichen sclerosis, anogenital pruritus	*Burning sensation with initial use may limit patient compliance
Vitamin D analogues	Inhibits TNF-a 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

Table 2

Topical corticosteroid formulations

Potency Class	Corticosteroid	Available formulations
I (Ultra High)	Clobetasol propionate 0.05% Halobetasol proprionate 0.05% Augmented betamethasone dipropionate 0.05% Fluocinonide 0.1% Diflorasone diacetate 0.05%	cream, ointment cream, ointment gel, ointment cream ointment
II (High)	Betamethasone dipropionate 0.05% Augmented betamethasone dipropionate 0.05% Desoximetasone 0.25% Amcinonide 0.1% Desoximetasone 0.05–0.25% Diflorasone diacetate 0.05% Fluocinonide 0.05%	ointment lotion, cream cream, ointment ointment gel, cream, ointment cream solution, gel, cream, ointment
III (Medium)	Betamethasone dipropionate 0.05% Betamethasone valerate 0.1% Amcinonide 0.1% Fluticasone propionate 0.005% Triamcinolone diacetate 0.5%	cream ointment cream ointment cream, ointment
IV (Medium)	Hydrocortisone valerate 0.2% Mometasone furoate 0.1% Triamcinolone acetonide 0.1%	ointment lotion, cream, ointment ointment
V (Medium)	Betamethasone valerate 0.1% Fluticasone propionate 0.05 Hydrocortisone butyrate 0.1% Hydrocortisone valerate 0.2% Triamcinolone acetonide 0.025–0.1%	cream cream solution, cream, ointment cream cream
VI (Low)	Alclometasone dipropionate 0.05% Desonide 0.05% Fluocinolone acetonide 0.01%	cream, ointment cream solution, cream
VII (Very Low)	Hydrocortisone 0.5–2.5%	lotion, cream, ointment

Table 3

Topical neuromodulatory anti-pruritic therapies

Therapy	Mechanism of action	Pruritic disorders with reported benefit	Comments
Topical anesthetics Lidocaine 2.5–5%, Prilocaine 2.5%	Blocks voltage gated Na channels	neuropathic pruritus, pruritus ani, postburn pruritus, notalgia paresthetica (NP)	*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, prurigo nodularis (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, uremic pruritus	*Efficacy demonstrated in pilot studies only *Not 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