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REVIEW

Novel Topical Treatments for Itch

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ABSTRACT

The experience of itch often poses a burden on patient quality of life and has the capacity to inflict significant suffering. Topical therapies are a mainstay of treatment for many cutaneous and systemic diseases and afford patients the opportunity to manage their conditions without many of the systemic side effects of non-topical therapies. We review a multitude of new topical medications targeting the skin, immune system, and neural receptors. The list includes Janus kinase inhibitors, tyrosine kinase inhibitors, phosphodiesterase inhibitors, transient receptor vanilloid inhibitors, topical cannabinoids, and topical acetaminophen. Many of the topical therapies reviewed show promising data in phase 2–3 clinical trials, but further research is needed to compare therapies head-to-head and test their efficacy on a broader range of conditions.

Keywords: New; Topical; Treatment; Itch; Pruritus

Key Summary Points

Itch poses a substantial burden on patient quality of life.

Topical therapies offer the unique ability to treat itch with minimal side effects.

We review a range of topical therapies targeting the skin, immune, and neural systems, and their effects on itch.

Many of the novel topical therapies we explored show promising clinical data with regards to reducing itch.

Further studies are warranted to evaluate the efficacy of these new topicals, spanning a range of conditions. Additionally, head-to-head comparison studies are needed to provide comprehensive insight into their effectiveness.

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INTRODUCTION

Itch is an unpleasant sensory phenomenon, and its chronic form has significant psychosocial

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impacts on patient quality of life. Numerous systemic and cutaneous pathologies produce the sensation of itch, and different mechanisms are implicated [1]. With this, there also exists a plethora of therapeutic targets for drug discovery. Research in pruritus is continually evolving as mechanisms of diseases are uncovered and clarified and as new and creative therapeutics enter the scientific community for investigation. The interplay between advancements in the understanding of disease mechanisms and data on the efficacy of novel drugs yields an expansive framework from which clinical decision-making in the management of pruritus may be derived.

Topical therapies in particular serve as a cornerstone of treatment for many dermatologic conditions as they often lack the systemic side effects that are present with systemic therapies. They are especially implicated as primary treatment modalities for conditions where the mechanism of disease is based in the skin; nevertheless, their role as adjunctive therapy in more systemic diseases is crucial. This review explores novel topical drug therapies that have recently emerged in the past few years and show potential for the treatment of pruritus, most commonly localized pruritus. We review a wide range of therapies, from drugs in preclinical phases of study to medications that have recently been introduced into clinical practice (Table 1).

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

TOPICAL JANUS KINASE INHIBITORS (BREPOCITINIB, DELGOCITINIB, RUXOLITINIB)

Topical Janus kinase (JAK) inhibitors have emerged as promising therapeutics in the treatment of pruritus owing to their efficacy and favorable safety profiles (Fig. 1). Their mechanism of action is immunomodulatory, involving inhibition of Janus kinases, which leads to disruption of signaling through type 2 cytokine, e.g., interleukin (IL)-4, IL-13, and IL-31, receptors as well as direct effects on cytokine receptors in nerve fibers [2].

Ruxolitinib

Topical ruxolitinib is a JAK1 and JAK2 inhibitor that was approved by the US Food and Drug Administration (FDA) in September 2021 for the treatment of atopic dermatitis and has shown efficacy in the treatment of associated atopic itch and other itchy conditions including psoriasis, lichen planus, and cutaneous graft-versus-host disease (GVHD).

Phase III trials showed ruxolitinib to be efficacious in treating atopic itch. The Topical Ruxolitinib Evaluation in Atopic Dermatitis Studies (TRuE-AD) comprise two randomized, double-blind, vehicle-controlled studies with the same design [3]. Both studies looked at individuals 12 years or older with atopic dermatitis for 2 years or more, an IGA score of 2 or 3, and a body surface of 3–20% not including the scalp [3]. Patients were randomized to receive twice daily 0.75% or 1.5% ruxolitinib cream or vehicle cream for the initial 8 weeks of the study [3]. Within the first 12 h of the first application of ruxolitinib cream, there were significant reductions in itch NRS scores compared to vehicle [3]. Additionally at week 8, in patients with baseline itch NRS scores ≥ 4, there were significantly more patients with clinically relevant improvements in scores in TruE-AD1 and TruE-AD2 in those treated with ruxolitinib 0.75% (40.4% and 42.7%, respectively) and ruxolitinib 1.5% (52.2% and 50.7%, respectively) compared to the vehicle (15.4% and 16.3%, respectively) [3]. By the second day, both studies showed a significantly greater proportion of patients achieving $\geq$ 4-point reductions on NRS in the ruxolitinib 1.5% cohort (TruE-AD1, 11.6%; TruE-AD2, 10.8%) versus the vehicle (TruE-AD1, 2.9%; TruE-AD2, 1.3%) [3].

Ruxolitinib has demonstrated efficacy in reducing disease severity in psoriasis but with no published data on itch [4]. Further study in this area is needed, but it is assumed that it would also work to reduce pruritus. Similarly, ruxolitinib has demonstrated efficacy in

Table 1 Summary of new topical treatments under investigation, their mechanism of action, and effects on itch

Drug	Mechanism of action	Efficacy in reducing pruritus
Brepocitinib	TYK2/JAK1 inhibitor	A statistically significant proportion of patients with AD receiving brepocitinib 1% once daily (45.2%), 3% once daily (50.0%), and 1% twice daily (40.7%) demonstrated ≥ 4-point reductions on the PP-NRS at 6 weeks compared to those receiving vehicle (daily, 18.2%; twice daily, 16.7%)
Ruxolitinib	JAK1 and JAK2 inhibitor	TruE-AD1 and TruE-AD2 phase III studies demonstrated that at week 8 in patients with baseline itch NRS scores ≥ 4, significantly more patients treated with ruxolitinib 0.75% (TruE-AD1, 40.4%; TruE-AD2, 42.7%) and ruxolitinib 1.5% (TruE-AD1, 52.2%; TruE-AD2, 50.7%) compared to vehicle (TruE-AD1, 15.4%; TruE-AD2, 16.3%) had clinically relevant improvement in scores
		Ruxolitinib 1.5% cream applied twice daily to lesional skin of patients with lichen planus resulted in reduced scores from baseline in Skindex-16 (from 56.2 to 19.8) and pruritus NRS (from 5.8 to 1.3) at week 4 in a phase 2 study of 12 patients
Delgocitinib	JAK1–3 and TYK2 inhibitor	Patients with AD applying 0.5% delgocitinib ointment twice daily reported a mean change in pruritus NRS of − 1.6 and − 1.3 at weeks 4 and 25, respectively
		Patients with mild to severe chronic hand eczema receiving 20 mg/g delgocitinib cream demonstrated early and sustained reductions in itch and clinically relevant reductions of ≥ 4 points in itch baseline were noted by week 16 in 48.4% of patients, compared to 17.9% of patients treated with vehicle cream
Roflumilast	PDE4 inhibitor	Roflumilast cream rapidly and effectively reduced itch severity in plaque psoriasis, providing improvements after 2 weeks with a reduction in worse itch of − 4 on a 10-point scale at week 8
		DERMIS-1 and DERMIS-2 phase III studies demonstrated that 67.5% and 69.4% of patients treated with roflumilast, and with baseline WI-NRS scores ≥ 4, had at least 4-point reduction in score (WI-NRS Success) compared to 26.8% and 35.6% of patients treated with vehicle cream, respectively
		A phase III trial demonstrated that in 8 weeks, 62.8% of patients treated with roflumilast for seborrheic dermatitis experienced WI-NRS Success compared to 40.6% of those treated with vehicle cream; this improvement was noted within 2 days of initial therapy
		INTEGUMENT-1 and INTEGUMENT-2 phase III studies showed significant reductions in WI-NRS within 1 month in patients with AD treated with 0.15% roflumilast cream; 33.6% and 30.2% of treated patients had significant improvements vs. 20.7% and 12.4% in the vehicle group in both studies, respectively, and improvements were noted as early as 1 day after initial application [20]
Lotamilast	PDE4 inhibitor	Statistically significant improvement in SCORAD-C in patients with AD treated with 0.2% lotamilast ointment compared to vehicle at week 4 with a − 50.0% and − 69.5% mean difference in the full analysis set and the per protocol set, respectively
		Greater decrease in pruritus score in patients with AD treated with lotamilast 0.2% compared to vehicle (− 37.5% vs. − 6.7%)
Difamilast	PDE4 inhibitor	In patients with AD, difamilast 1% improved pruritus VAS scores from baseline within the first week (− 36.4% mean change) compared with placebo
		Early, sustained improvement in pruritus VAS scores in patients with AD treated with difamilast, with changes in least square means of − 18.00, − 17.21, and 8.19 in difamilast 0.3%, difamilast 1%, and vehicle, respectively, at week 4
		Patients with AD treated with difamilast 0.3% and difamilast 1% twice daily for 1 week had least square mean changes of − 0.59 and − 0.54, respectively, compared to − 0.14 in the vehicle group; these differences were statistically significant and persisted until week 4
		At 1 week, patients with AD treated with difamilast 1% ointment had a significantly greater change of least square mean from baseline compared to vehicle, and by week 4, the change was − 0.65 vs. − 0.04 in the difamilast 1% cohort compared vehicle, respectively
LEO 29102	PDE4 inhibitor (selective for PDE4D isoform)	Patients with AD treated with 0.3 mg/g and 2.5 mg/g of LEO 29102 twice daily had the greatest percentage of patients with absent pruritus after 4 weeks (28.0% and 23.3%, respectively)
Asivatrep	TRPV1 antagonist	Significantly greater mean change in patient-reported pruritus VAS scores from baseline in patients with AD treated with asivatrep compared to vehicle (− 2.3 points vs. − 1.5 points)

Table 1 continued

Drug	Mechanism of action	Efficacy in reducing pruritus
Cannabidiol	Modulation of cannabinoid receptors and TRP channels	14-day application of topical cannabidiol in patients with AD resulted in statistically significant reductions in pruritus VAS (pre-treatment, 5.78; post-treatment, 4.01) and 5-D pruritus scale (pre-treatment, 13.2; post-treatment, 10.86)

JAK Janus kinase, *TYK* tyrosine kinase, *PDE* phosphodiesterase inhibitor, *TRPV* transient receptor potential vanilloid, *AD* atopic dermatitis, *PP-NRS* Peak Pruritus Numerical Rating Scale, *SCORAD-C* Scoring Atopic Dermatitis C, *VAS* visual analog scale

treating lichen planus (LP) in a phase 2 study [5]. The study investigated 12 patients with LP; ruxolitinib 1.5% cream was applied twice daily to LP lesions for 8 weeks except for an untreated index lesion that served as a control [5]. The results showed that patient-reported quality of life and symptoms of pruritus were rapidly improved following treatment with ruxolitinib on the Skindex-16 and pruritus NRS, respectively [5]. By week 2, average scores on both scales were decreased by more than half and progressively decreased throughout the duration of the treatment period [5]. At week 4, Skindex-16 and pruritus NRS were reduced from baseline scores of 56.2 and 5.8 to 19.8 and 1.3, respectively [5]. Although the mechanism of itch is unclear in LP, some evidence points to the role of JAK1 and/or JAK2 [5, 6].

Additionally, topical ruxolitinib has been studied in the management of cutaneous GVHD with good efficacy on disease severity [7]. Patients with cutaneous GVHD often complain of pruritus, but the pathophysiology of itch in this condition is not well elucidated and the severity of itch has been reported not to be associated with disease severity [8]. There is a reported association between the reduction of pruritus and a longer failure-free survival in patients with chronic GVHD, pointing to the need for further research in this area [8, 9]. Numerous studies are currently underway to evaluate ruxolitinib's efficacy in other itchy conditions including prurigo nodularis, lichen sclerosus, and seborrheic dermatitis.

Brepocitinib

Brepocitinib, a small-molecule tyrosine kinase 2 (TYK2)/JAK1 inhibitor is among the novel drugs in this category. A recent phase 2b randomized, double-blind, vehicle-controlled, dose-ranging, and parallel group study evaluated its use in patients with mild to moderate atopic dermatitis [10]. The study utilized the Peak Pruritus Numerical Rating Scale (PP-NRS) in 241 patients; this is a single-item survey designed to inquire about a patient's worst itch over the preceding 24 h on a scale of 0 (no itch) to 10 (worst itch imaginable) [11]. Across all treatment dosages including brepocitinib 0.1% once daily, 0.3% once or twice daily, 1.0% once or twice daily, and 3.0% once daily, there was a numerically higher proportion of participants with $\geq$ 4-point reductions in weekly average of the PP-NRS from week 3 to week 6, the end of the study period, compared to vehicle groups (once or twice daily). However, statistically significant differences in $\geq$ 4-point reductions on the PP-NRS were noted at week 6 in the brepocitinib 1% once daily (45.2%), 3% once daily (50.0%), and 1% twice daily (40.7%) treatment groups compared to vehicles (daily, 18.2%; twice daily, 16.7%) [10].

Delgocitinib

Delgocitinib, a JAK1–3 and TYK2 inhibitor, that has been approved for pediatric and adult atopic dermatitis in Japan is another novel topical that has shown some evidence in alleviating atopic pruritus [12]. A phase 3, randomized, double-blind, vehicle-controlled study and an open-label, long-term extension study evaluated the use of delgocitinib 0.5% ointment applied twice daily for the treatment of patients with moderate to severe AD as determined by a modified eczema area and severity index score $\geq$ 10, an investigator global assessment (IGA) score of 3 or 4, and a body surface area of 10–30% [13]. This was performed for 4 weeks followed by a

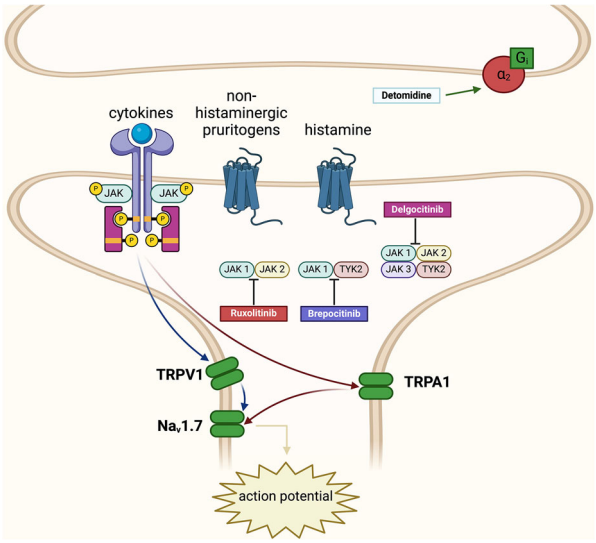

Fig. 1 Overview of the JAK/STAT pathway's role in generating action potentials after binding of cytokines and the mechanism of action of topical JAK inhibitors. Detomidine activates skin nociceptor α2-adrenergic receptors, reducing itch signaling (Created with BioRender.com). *JAK* janus kinase, *TRPV1* transient receptor potential vanilloid subfamily V member 1, *TRPA1* transient receptor potential ankyrin 1

continuation period of 24 weeks [13]. The trial evaluated changes in pruritus NRS during the daytime and nighttime and found that in as early as the nighttime of the first day, patients applying the delgocitinib ointment saw a statistically significant reduction in pruritus NRS score compared to the vehicle ointment; this change was maintained over time [13]. Moreover, the mean change in pruritus NRS at week 4 was − 1.6 and the change at week 25 was − 1.3 [13]. Nevertheless, despite these improvements in NRS scores, the level of change is not considered clinically significant [14].

Delgocitinib has also demonstrated efficacy in the management of chronic hand eczema [15]. One phase 2b dose-ranging double-blind randomized clinical trial evaluated 258 adults with mild to severe chronic hand eczema [15]. Patients were randomized to delgocitinib cream 1, 3, 8, or 20 mg/g or a vehicle cream applied twice daily for 16 weeks. Eleven signs and symptoms of chronic hand eczema were evaluated through a Hand Eczema Symptom Diary on an 11-point rating scale [15]. Application of 20 mg/g delgocitinib cream resulted in early and sustained reductions in of both itch and pain [15]. Clinically relevant reductions of ≥ 4 points in itch and pain from baseline were noted by week 16 in 48.4% and 63.6% of patients, respectively, compared to 17.9% and 5.9% of patients treated with vehicle cream [15]. Furthermore, there were statistically significant improvements in all chronic hand eczema signs and symptoms in this treatment group compared to the vehicle cream [15]. Clinician-reported outcomes corroborated this data [15].

PHOSPHODIESTERASE 4 INHIBITORS (ROFLUMILAST, DIFAMILAST, LOTAMILAST, LEO 29102)

Phosphodiesterase 4 (PDE4) catalyzes the metabolism of cyclic adenosine 3′,5′-monophosphate (cAMP), resulting in enhanced production of proinflammatory cytokines and chemokines [1]. Elevated cAMP levels, by inhibiting PDE4, may reduce inflammation and itch in various disorders including AD. Topical PDE4 inhibitors include crisaborole, roflumilast, lotamilast, difamilast, and LEO 29102.

Roflumilast

Roflumilast cream was FDA approved for plaque psoriasis in July 2022, as it rapidly and effectively reduced itch severity, providing improvement after 2 weeks with a reduction in worst itch of − 4 on a 10-point scale at week 8 [16, 17]. Furthermore, in two pivotal phase III trials, DERMIS-1 and DERMIS-2, 67.5% and 69.4% of patients treated with roflumilast and with baseline WI-NRS scores ≥ 4 had at least a 4-point reduction in score (WI-NRS Success) compared to 26.8% and 35.6% of patients treated with vehicle cream, respectively [18]. In December 2023, roflumilast 0.3% was approved for the treatment of seborrheic dermatitis. A phase III trial demonstrated that in 8 weeks, 62.8% of patients treated with roflumilast for

seborrheic dermatitis experienced WI-NRS Success compared to 40.6% of those treated with vehicle cream; this improvement was noted within 2 days of initial therapy [19]. Roflumilast is also currently being studied for AD. Two phase III trials, INTEGUMENT-1 and INTEGUMENT-2, showed significant reductions in WI-NRS within 1 month in patients with AD treated with 0.15% roflumilast cream; 33.6% and 30.2% of treated patients had significant improvements versus 20.7% and 12.4% in the vehicle group in both studies, respectively, and improvements were noted as early as 1 day after initial application [20].

Difamilast

Difamilast is another topical PDE4 inhibitor approved in Japan in September of 2021 for the management of AD in adults and children greater than the age of 2. Difamilast 0.3%, difamilast 1%, or placebo was administered twice daily for 8 weeks in a phase 2 clinical trial for patients with mild or moderate AD (baseline IGA score of 2 or 3 and a 3-year history of disease) and 10–70 years of age. Regarding pruritus, difamilast 1% improved pruritus visual analog scale (VAS) scores from baseline within the first week (− 36.4% mean change) compared with placebo. Itch improvement was sustained, with a reduction of VAS scores throughout the 8 weeks of the study [21]. Another phase 2 clinical trial looked at Japanese pediatric patients 2–14 years old. This was a randomized, double-blind, placebo-controlled, 4-week study to evaluate the safety and efficacy of difamilast for AD [22]; 73 patients were randomized to treatment with difamilast 0.3%, difamilast 1%, or vehicle ointment twice daily. Patients receiving difamilast showed a consistent improvement in VAS pruritus scores over the trial period; such improvements were evident as early as week 1 where patients treated with difamilast 0.3% and 1% had least square mean changes from baseline of − 18.61 and − 12.83, respectively, compared to 0.34 in patients treated with vehicle [22]. By week 4, changes in least square means were − 18.00, − 17.21, and 8.19 for difamilast 0.3%, difamilast 1%, and vehicle, respectively [22].

Two phase 3 trials similarly highlight the efficacy of difamilast in treating pruritus. One double-blind, vehicle-controlled phase 3 trial looked at difamilast for the treatment of atopic dermatitis in patients aged 2–14 years. Patients received difamilast 0.3%, difamilast 1%, or vehicle ointment twice daily for 4 weeks [23]. Using a pruritus visual rating score, at week 1, patients treated with difamilast 0.3% and difamilast 1% had least square mean changes of − 0.59 and − 0.54, respectively, compared to − 0.14 in the vehicle group; these differences were statistically significant and persisted until week 4 of the study [23]. Another randomized, double-blind, vehicle-controlled phase 3 trial looked at a Japanese cohort of patients aged 15 to 70 years old with atopic dermatitis. Patients were treated with difamilast 1% ointment or vehicle twice daily for 4 weeks [23]. At week 1, there was a significantly greater change of least square mean from baseline in patients treated with difamilast 1% compared to vehicle, and by week 4, the change was − 0.65 in the difamilast 1% cohort compared to − 0.04 in the vehicle group, which was statistically significant [23].

Lotamilast

Lotamilast is another PDE4 inhibitor that has garnered attention. One multicenter, randomized, vehicle-controlled phase 2 clinical trial evaluated patients with AD aged 20 to 64 years with an affected body surface area of 5–30%. Patients received 0.2% lotamilast or vehicle ointment for 4 weeks, and those who continued for the extension phase received 0.2% lotamilast for an additional 8 weeks [24]. Pruritus scores were evaluated using Scoring Atopic Dermatitis C (SCORAD-C), which showed statistically significant improvements after 4 weeks [24]. There was a − 50.0% and − 69.5% mean difference between lotamilast and vehicle in the full analysis set and per protocol set, respectively [14, 24]. A randomized, vehicle-controlled, exploratory trial on Japanese children with AD also found lotamilast to be efficacious in the reduction of pruritus [25]. In this study,

62 patients were treated with lotamilast 0.05%, lotamilast 0.2%, or vehicle ointment twice daily for 2 weeks [25]. Notably, the trial found a greater decrease in pruritus score in those treated with lotamilast 0.2% compared to vehicle (− 37.5% vs. − 6.7%) [25].

LEO 29102

LEO 29102 is a PDE inhibitor selective for the PDE4D isoform that has also been studied in patients with AD [14]. A proof of concept phase 2 trial compared the efficacy of LEO 29102 to pimecrolimus in patients with AD. Patients were treated with LEO 29102 dosages of 0.03 mg/g, 0.1 mg/g, 0.3 mg/g, 1.0 mg/g, and 2.5 mg/g twice daily [14]. Pruritus was evaluated using the descriptors absent, mild, moderate, and severe to describe itch on the trunk and limbs [14]. The study found that patients treated with 0.3 mg/g and 2.5 mg/g of LEO 29102 twice daily had the greatest reductions in pruritus after 4 weeks (28.0% and 23.3%, respectively), although the statistical significance of the results was not reported [14].

ARYL HYDROCARBON ACTIVATOR (TAPINAROF)

Activation of the aryl hydrocarbon receptor (AHR) induces epidermal differentiation and has implications in skin barrier repair [26]. Tapinarof is a topical agent that activates AHR and has been FDA approved in a 1% formulation for the treatment of plaque psoriasis. Two phase III trials on patients with mild to severe plaque psoriasis showed a highly significant difference in patients achieving itch-free status compared to controls in 12 weeks (50% in both trials compared to 32% and 27% in the vehicle groups, respectively) [27]. Tapinarof has also been studied in AD in two phase III trials ADORING 1 and 2. Both trials showed substantial amounts of patients achieving meaningful itch reductions in those treated with tapinarof compared to vehicle by week 8 (ADORING 1, 55.8% vs. 34.2%, respectively; ADORING 2, 52.8% vs. 24.1%, respectively) [28, 29].

TRPV1 ANTAGONIST (ASIVATREP)

TRPV1 is strongly implicated in acute itch via histamine inhibition and also plays a role in non-histaminergic pruritus and chronic itch via activation of protease-activated receptors and subsequent neurogenic inflammation [25, 30–32].

Asivatrep or PAC-14028 is a selective and potent transient receptor potential vanilloid subfamily V member 1 (TRPV1) antagonist [33]. In a randomized, double-blind, vehicle-controlled phase 2b trial, patients with mild to moderate AD were randomized to receive vehicle cream or asivatrep 0.1%, 0.3%, and 1% applied twice daily for 8 weeks. All asivatrep-treated groups showed decreased mean change in VAS from baseline over the course of the study, although this difference was only statistically significant from baseline at week 8 in the asivatrep 1% group [34]. In a randomized, vehicle-controlled, phase 3 trial, patient-reported assessments of itch were lower in patients with AD treated with asivatrep cream than those receiving vehicle at week 1 and maintained until the end of the study (week 8). Moreover, the mean change in patient-reported pruritus VAS scores from baseline were significantly greater in the asivatrep-treated patients compared to those receiving vehicle (− 2.3 points vs. − 1.5 points), indicating significant improvement in itch [33]. Additionally, asivatrep appears to optimize skin barrier function through its production of epidermal differentiation markers, which may contribute to its antipruritic effect [33].

TOPICAL CANNABINOIDS (CANNABIDIOL)

Cannabinoids are compounds that act on the endocannabinoid system to elicit a range of physiologic effects. Recently, topical cannabinoids have garnered attention for their potential role in managing cutaneous pathologies, namely AD, as they have been shown to have antipruritic and anti-inflammatory properties through activity on neurons, inflammatory cytokines, and mast cells [35]. The antipruritic

mechanism of action is likely multifactorial, including peripheral and central modulation of cannabinoid receptors 1 (CB1) and 2 (CB2) and TRP channels [35]. The central effect is predominantly mediated via CB1, and the peripheral effect likely involves an analgesic effect mediated by both CB1 and CB2 [35].

Cannabidiol

A recent study investigated the effects of topical cannabidiol on 14 patients with AD aged 25–-73 years old [36]. Patients completed surveys before and after 14-day application [36]. Pruritus was assessed using VAS-pruritus, which assessed patients' itch on a scale of 0 (no itch) to 10 (worst itch of their life), and the 5-D pruritus scale, which assesses the degree, duration, disability, and distribution of itch within the prior 2 weeks [36]. Patients experienced a statistically significant reductions in pruritus on both, the VAS-pruritus (pre-treatment, 5.78; post-treatment, 4.01) and the 5-D pruritus scale (pre-treatment, 13.2; post-treatment, 10.86) [36].

Another study evaluated the effects of topical cannabinoid gel in patients with self-reported eczema. Twenty individuals consented to participate, of whom 16 completed the Patient Oriented Eczema Measure to assess disease severity and the emotional domain of the Quality-of-Life Hand Eczema Questionnaire to assess the psychosocial burden of disease [37]; 67% of participants reported a decrease in itch and more than 60% had a perceived improvement in their eczema [37].

Additionally, a role for topical cannabinoids has been suggested in uremic pruritus. There is some evidence to show their effect on TRPV1, which is implicated in the pathogenesis of uremic pruritus [38]. In one non-randomized study, 21 individuals with uremic pruritus were treated with a cream containing the endogenous cannabinoid acetylethanolamide and a related noncannabinoid, palmitoylethanolamide, which resulted in 38% of participants experiencing complete relief of pruritus [38, 39]. More studies are needed to further elucidate the role of cannabinoids for pruritus.

DRUGS IN EARLY PHASE OF TESTING (B244, DETOMIDINE, KM001, TOPICAL ACETAMINOPHEN)

B244

B244 is a live biotherapeutic currently under investigation for a role in the management of AD (Table 2). B244 consists of a purified strain of *Nitrosomonas eutropha* [40]. This is an bacteria that oxidizes ammonia to nitrite and nitric oxide, which is thought to promote antimicrobial and anti-inflammatory activity, respectively [40]. In vitro analysis found B244 to reduce Th2 cytokines associated with AD including IL-4, IL-5, and IL-13 [40]. A randomized, double-blind, placebo-controlled, dose-ranging, phase 2b trial of B244 enrolled 547 patients 18–65 years old with mild to moderate AD and moderate to severe pruritus [40]. Optical density (OD) at 600 nm was used to divide patients into a low dose group (OD 5.0), a high dose group (OD 20.0), or a vehicle group for a 4-week treatment period and 4-week follow-up period [40]. Patients were to apply a topical spray twice daily during the treatment weeks [40]. Pruritus was assessed using the WI-NRS at 4 weeks [40]. Patients treated with B244 saw a 34% reduction in WI-NRS score (B244, − 2.8; placebo, − 2.1) from a baseline score greater than 8; this was statistically significant [40].

Topical Detomidine (CLE 400)

CLE-400 is a topical gel that contains detomidine, an activator of skin nociceptor α2-adrenergic receptors, which is proposed to inhibit receptor excitability and ultimately reduce neuropathic itch signaling [41]. CLE-400 is undergoing phase 2 studies for notalgia paresthetica [41].

KM001

There is evidence to suggest the involvement of TRPV3 in pruritus pathways. As such, this receptor has garnered attention as a potential

Table 2 Emerging new topical treatments under investigation, their proposed mechanism of action, and effects on itch

Drug	Proposed mechanism of action	Efficacy in reducing pruritus
B244 (NCT04490109)	Purified strain of ammonia-oxidizing bacteria *Nitrosomonas eutropha*; potential antimicrobial and anti-inflammatory with reduction in Th2 cytokines (IL-4, IL-5, and IL-13)	Statistically significant 34% reduction in WI-NRS score (B244, − 2.8; placebo, − 2.1) from a baseline score > 8 in mild to moderate AD and moderate to severe pruritus
Topical detomidine (CLE 400)	Activates skin nociceptor α2-adrenergic receptors	Currently under preclinical investigation with pruritus models; reports of a cumulative analgesic effect with repeated dosing
KM001 (NCT05454462)	TRPV3 antagonist	Currently under investigation in phase 2 trials for the treatment of lichen simplex chronicus
Topical acetaminophen (NCT03997851)	Inhibition of cyclooxygenase pathway and prostaglandin synthesis	Individuals treated with the 2.5% and 5% acetaminophen gel had significant reductions in histamine and cowhage-evoked itch compared to vehicle, with significantly reduced mean peak itch intensity with 2.5% gel compared to vehicle (− 3.9 vs. − 5.8)

IL interleukin, *WI-NRS* Worst Itch Numerical Rating Scale, *AD* atopic dermatitis

therapeutic target for itch. Notably, KM001 has emerged as a novel topical small-molecule inhibitor of TRPV3 and is currently undergoing phase II trials for the treatment of lichen simplex chronicus [30].

Topical Acetaminophen

Topical acetaminophen has recently been studied for a possible role in treating itch. Traditionally, the mechanism of action is thought to involve inhibition of the cyclooxygenase pathway and prostaglandin synthesis, although the exact mechanism is not entirely known [42]. In a double-blind, vehicle-controlled pilot study, 17 healthy volunteers 19–50 years of age (average age of 26.4 years) were evaluated for treatment response with 1%, 2.5%, and 5% acetaminophen gels and a vehicle gel that was applied to the skin prior to the induction of itch with histaminergic (with histamine) and non-histaminergic (with cowhage) stimuli. Individuals treated with the 2.5% and 5% acetaminophen gel formulations had significant reductions in itch for histamine and cowhage compared to vehicle [42]. Moreover, the mean peak itch intensity was significantly reduced with the 2.5% gel formulation by 32% compared to the vehicle [42].

CONCLUSION

Topical treatments are the mainstay of therapies used by dermatologists; however, there were limited developments of novel topical antipruritics. The significant advancement in our understanding of the mechanisms of itch is leading to the development of novel topical therapies for itch, namely localized itch. The therapies highlighted carry a wide range of mechanisms and varying degrees of efficacy in their respective phases of study, inspiring continued innovation to target itch pathways. Comparisons between the drug therapies discussed may be limited by differences in study methods, phases of clinical trials, and pruritus assessment tools. For this reason, it is difficult to determine if one drug is more efficacious than another without being tested in a head-to-head

trial. Furthermore, AD is the most studied condition in this review, and there is more room to test these topicals in the management of other itchy conditions. Ultimately, as research in the field continues to grow, increasing therapeutics are becoming available, allowing for more patient options and increasingly nuanced modalities of clinical practice.

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Declarations

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