Management of Itch in Atopic Dermatitis

Judith Hong, MD[*], **Joerg Buddenkotte, PhD**[*,†], **Timothy G. Berger, MD**[*], and **Martin Steinhoff, MD, PhD**[‡]

[*]Department of Dermatology, University of California San Francisco, San Francisco, CA

[†]Department of Surgery, University of California San Francisco, San Francisco, CA

[‡]Department of Dermatology, University Hospital, Münster, Münster, Germany

Abstract

Atopic dermatitis is a common, pruritic, inflammatory skin disorder. Chronic, localized, or even generalized pruritus is the diagnostic hallmark of atopic dermatitis, and its management remains a challenge for physicians. The threshold for itch and alloknesis is markedly reduced in these patients, and infections can promote exacerbation and thereby increase the itch. Modern management consists of anti-inflammatory, occasionally antiseptic, as well as antipruritic therapies to address the epidermal barrier as well as immunomodulation or infection. Mild forms of atopic dermatitis may be controlled with topical therapies, but moderate-to-severe forms often require a combination of systemic treatments consisting of antipruritic and immunosuppressive drugs, phototherapy, and topical compounds. In addition, patient education and a therapeutic regimen to help the patient cope with the itch and eczema are important adjuvant strategies for optimized long-term management. This review highlights various topical, systemic, and complementary and alternative therapies, as well as provide a therapeutic ladder for optimized long-term control of itch in atopic dermatitis.

Pruritus or itch, which is defined as an unpleasant sensation that elicits an urge to scratch,[1] is such an integral part of atopic dermatitis (AD) that it is a major characteristic in the diagnostic criteria and a hallmark of AD.[2] AD has been called the "itch that rashes,"[3] which reflects how important it is to pay attention to pruritus in the management of AD. Pruritus can lead patients to scratch until they are bleeding, and scratching in turn can aggravate the skin disease. Nocturnal scratching is a common issue that can result in sleep disturbances and a dramatic impairment in the quality of life in these patients. In addition, psychological disturbances, such as stigmatization and social isolation,[4] are also detriments to quality of life.[5] In this article we briefly summarize current knowledge of the pathophysiology and trigger factors of AD and focus in-depth on the various types of treatments for short-term and long-term management of itch in AD.

Pathophysiology of Itch in AD

The sensation of pruritus can be triggered by endogenous and exogenous stimuli, which activate specific peripheral un-myelinated C-fiber nerve endings in the epidermis and dermis. The pruritogenic stimulus is then signaled along the dorsal root ganglion (which

harbors the RNA and generates the proteins expressed by or released from the cell surface of nerve-endings) via the spinal cord before it crosses the contralateral spinothalamic tract, reaching different areas of the cortex. In the cortex, the scratching reflex is initialized in the motor-cortex and associated motor-cortex. Other cortical and subcortical regions can modulate the itch response, leading to "sensitized skin" and itch-associated mood changes, for example.[6,7] Thus, the central nervous system modulates the perception of "itch" and triggers the desire to scratch. Various mediators of pruritus in AD interact with the pruritoception pathway at different levels. For example, in lamina 1 of the dorsal horn, the gastrin-releasing peptide receptor plays a role in mediating itch sensation in the spinal cord.[8,9] The receptor for substance P (SP), the neurokinin-1 receptor, is also highly expressed by lamina 1 neurons, which appears to be crucial for the transmission of itch to the brain.[6] Cutaneous inductors of itch include histamine,[10] proteases,[11–13] neuropeptides (eg, SP),[14,15] acetylcholine (in atopic patients),[16] cytokines,[17] neurotrophin-4,[18] platelet-activating factor,[19] endothelin, and certain leukotrienes.[20] Of note, changes in the plasticity and receptor density, as well as neuronal sensitization, may also be involved in AD pruritus.[21] The skin lesions in AD often have increased density of peripheral nerve fibers, including substance P-positive nerve fibers.[22] In addition, noxious stimuli, such as bradykinin in the lesional skin of AD patients, have been demonstrated to provoke itch instead of pain, suggesting complex but poorly understood interactions between itch and pain fibers.[23–25] TH2-derived cytokines may be involved in crosstalk between nerves and T lymphocytes, indicating a role of cytokines in itch and neuronal regulation.[6,26,27] For an in-depth study, we refer to other recent reviews focusing on the pathophysiology of itch in AD.[28–30]

Overview: Treatment Options in AD

Because itch is such a prominent and distressing aspect of AD, proper treatment of AD should involve the evaluation and management of any associated pruritus. Because of the complex pathophysiology of pruritus in AD and the impact of pruritus on patient's lives, dermatologists need to recognize and address various aspects of itch, including: (1) identification and elimination of trigger factors; (2) maintaining the skin barrier through emollients and occasional additives; (3) targeting inflammation through topical medications, systemic medications, or phototherapy; (4) symptomatic management of itch with other treatments that are not antiinflammatory; (5) addressing psychological and behavioral components; and (6) educating the patient (Table 1). The use of multidisciplinary clinics or centers will be discussed in further detail because they provide a setting where all these issues can be addressed. It is important for clinicians to "treat the patient, not just the disease" through an approach that integrates medication, education, and support.

Identification and Elimination of Trigger Factors

Identifying and eliminating trigger factors are crucial for the management of itch in AD. Sweating is generally considered one of the most common trigger of itch in AD,[31] and increased sweating has been observed in AD patients with lichenified skin.[32] Acetylcholine and vasoactive intestinal peptide may play a role because both regulate sweat gland function and have been found to be increased in the skin of AD patients.[33] The main methods to manage this frequent trigger factor are avoidance of activities that lead to pronounced sweating or immediate washing and cooling after exercising. Anticholinergic drugs do not appear to have an impact on pruritus and can be avoided,[34] supporting the idea that neuropeptides, such as vasoactive intestinal peptide and probably yet unknown mediators, are more important in triggering sweating in patients with AD.

Exogenous factors, such as contact with wool, can elicit pruritus in AD.[35,36] It is recommended that patients avoid wool and wear fabrics like cotton. Small studies of silver-coated textiles report decreasing staphylococcus colonization and pruritus in patients with AD, combining an anti-infectious as well as wool-avoiding approach.[37,38] Soaps and solvents are other exogenous irritants that can induce xerosis and thereby trigger itch.[39,40] Climate, environmental, and seasonal changes have been known to affect patients with AD.[41,42]

Aeroallergens, such as dust mites, pollen, and animal exposure (especially cat dander), are potential triggers of AD and have been shown to cause eczematous reaction with patch testing.[43] The use of dust mite reduction measures (e.g., mattress covers or vacuuming) remains controversial. Although mixed evidence exists that such measures reduce pruritus in AD,[44–46] some authors have recommended dust mite-reduction measures, including dust-mite mattress encasings and hot washing and drying of sheets and pillows every 6–8 weeks.[47]

Food allergies are another controversial trigger for AD. Food allergies can potentially exacerbate AD in two ways. The first is an immediate-type I allergic reaction within two hours after food allergen intake, provoking pruritus and/or erythema, subsequently leading to scratching and secondary exacerbation of eczematous lesions.[48] This immediate-type I reaction is triggered most commonly by hen's eggs or cow's milk in younger children.[49] The second is a delayed type-I allergy occurring 2–6 hours after ingestion of food, which directly causes the development of eczematous lesions. This reaction is much more uncommon than the immediate-type reaction and tends to occur with the ingestion of soy and wheat.[50,51]

Despite the known interaction between food allergens and cutaneous reactions, there is insufficient evidence that exclusion diets in unselected patients improve AD or the pruritus associated with AD.[52] In general, a thorough individual history and clinical correlation has to be taken into account before drastic dietary changes are considered. Food allergies are not a common AD trigger in older children and adults[53] because most children outgrow their food allergies.[54] Should food allergy be suspected as a trigger for AD (after consistent skin care and inflammation management), patients should be evaluated by specialists who can critically examine test results and recommend an individually-adapted diet. If a true food allergen is found, exclusion diets should also be pursued under the guidance of professionals because of certain risks, such as malnutrition.[55]

One should also consider infectious triggers in the management of AD, particularly *Staphylococcus aureus*.[56] In approximately 90% of patients, *S aureus* is the predominant microorganism in AD lesions.[57] The severity of eczema has been correlated with colonization of *S aureus*.[58,59] In general, systemic antibiotics (particularly antistaphylococcal agents) are considered important for treating exacerbations of AD secondary to bacterial infection.[60–62] However, the overall role of a preventive or systemic antibacterial therapy in management of AD, particularly if there is no overt secondary infection, remains controversial.[63,64] Other secondary infections implicated as disease factors in AD include streptococcal infections, yeasts, and viruses.[65] Moreover, the inappropriate use of topical antibiotics should be avoided because of the potential for resistance and allergies. Water-based antiseptics, such as polyhexamethylene biguanide, show a positive antiseptic effect with a very low or no side effect profile for resistance and allergic/toxic reactions.[66] In general, identifying and controlling or eliminating trigger factors are important parts of AD patient visits, and patients and family members should be educated about these factors (Table 2 and the section "Patient Education" in this article).

Topical Therapies

Topical therapies are a fundamental part of the armamentarium of dermatologists. Topicals are often used as a first-line therapy in AD because they usually have a lower risk of adverse effects than the systemic medications used in AD therapy.

Our discussion of topical therapies in the management of itch in AD is divided into 3 parts: (1) emollients; (2) antiinflammatory agents, specifically corticosteroids, calcineurin-inhibitors, and coal tar; and (3) other antipruritic agents that do not directly target inflammation, specifically menthol, topical doxepin, and topical naltrexone.

Emollients

Barrier dysfunction is a key issue to address for long-term treatment of AD[67] because atopic skin is characterized by heightened transepidermal water loss and decreased ceramide levels, which may result in decreased water content.[68] Reduction in stratum corneum lipids (e.g., ceramides)[69] and filaggrin defects[70] are some, but probably not all, barrier defects in AD skin. Moisturizers play an important part in the management of AD[71] and can help to reduce pruritus.[72] Emollients may serve as steroid-sparing agents. Studies have shown a decrease in the need for topical corticosteroids while maintaining efficacy in treatment of AD.[73–75] Emollients have also been shown to enhance the efficacy of topical corticosteroids, including their effects on pruritus.[76,77] More recently, ceramide-based emollients have been developed for the management of atopic dermatitis.[78] In a randomized, investigator-blinded trial, investigators compared a ceramide-dominant, triple-lipid barrier repair formulation to fluticasone cream, and they found that both groups demonstrated similar improvements in pruritus.[79] Despite the wide variety of prescription medications available, emollients remain a fundamental part of the management of AD and pruritus. It is important to encourage patients to use moisturizing ointments or modern moisturizing creams instead of classical creams or lotions that do not moisturize. Every AD patient should be educated on gentle skin care using emollients.

Antiinflammatory Topical Agents

Antiinflammatory agents are valuable for managing pruritus in AD because the overall severity of inflammation correlates with the severity of pruritus.[80] Therefore, successful treatment of the underlying inflammation of the disease will often help to relieve associated symptoms. Early and effective use of antipruritic agents may prevent exacerbation and induction of eczema lesions. A proactive prevention of lesion rebound by the twice-weekly application of antiinflammatory agents may be an important part of maintenance therapy in AD.[81]

Topical Glucocorticosteroids (GCs)

Topical GCs are a mainstay of antiinflammatory AD treatment. Therapy can be customized according to person, preference, and anatomical location, with potencies ranging from low (class 7) to high (class 1) and different vehicles (e.g., ointments, creams, gels, oils, foams and sprays).[82] Topical corticosteroids have been shown not only to improve the overall severity of disease, but also excoriations and/or pruritus.[83–87]

Topical corticosteroids (typically diluted) can also be used in conjunction with wet wrap therapy, in which topical corticosteroids are applied to the body followed by a layer of wet clothing and then a dry layer.[88] Investigators have shown that wet wraps with steroids improve various aspects of AD, including pruritus and/or excoriations. Side effects reported include chills, folliculitis, and impetigo, with a rarer incidence of cutaneous pseudomonas infection, herpetic infections, and adrenal suppression.[89–92] Wet wraps are generally not

used as first-line treatment, but are a useful option in patients with severe or recalcitrant AD with itch.[89,92]

Topical Calcineurin Inhibitors (TCIs)

TCIs are another treatment option for AD and do not possess the risks of skin atrophy and adrenal suppression that are associated with topical GCs. Topical tacrolimus (Protopic, 0.1% and 0.03% ointment) and topical pimecrolimus (Elidel 1%) are approved by the Food and Drug Administration (FDA) for the treatment of AD. Studies in both adult and pediatric AD patients have demonstrated significantly reduced pruritus with tacrolimus ointment.[93,94] In a recent study, investigators evaluated the efficacy of tacrolimus ointment for itch reduction in children with AD with the use of a wrist movement monitor (DigiTrac) to track nocturnal scratching. The seven patients showed marked reduction in self-reported itch and nocturnal scratching.[95]

When tacrolimus ointment has been compared with pimecrolimus cream, tacrolimus had greater efficacy in reducing AD-associated pruritus.[96,97] Moreover, use of 0.1% tacrolimus ointment resulted in a greater reduction in pruritus than 1.0% hydrocortisone acetate ointment[98] and 0.1% aclometasone diproprionate[99] and was similar in efficacy to 0.1% hydrocortisone-butyrate ointment.[100] The most common side effects reported from TCI[1] were skin burning (transient at the beginning of therapy), pruritus, and skin erythema.[93–98]

The transient burning can be prevented by an application of 5% lidocaine gel 20 minutes before the application of tacrolimus. In a recent systemic review, tacrolimus ointment was effective for treatment of itch in AD, had a rapid onset of pruritus reduction (usually within four days of initiation), had an effect duration lasting several months, and was safe for long-term use.[101] Overall, tacrolimus, and to a lesser extent pimecrolimus, are useful topicals for short-term and long-term treatment of pruritus in AD.

Coal Tar

Coal tar has a long history of use in the treatment of inflammatory skin diseases. It comes in a variety of formulations, including ointments, creams, lotions, gels, shampoos, and solutions and is often compounded with topical steroids or an emollient.[102] The mechanism of action of coal tar is not well understood, but it appears to have antibacterial, antifungal, antipruritic, and antiinflammatory effects.[103,104]

Although there are few publications and no placebo-controlled trials on coal tar efficacy in AD,[105–108] it remains a useful second-line topical medication. Two trials reported improvement in scoring systems that included excoriations,[105–108] and the authors of one trial demonstrated improvement in a scoring system that included pruritus.[108] We commonly compound 20% coal tar (LCD) in a petrolatum base ("gold tar"), or 3%–5% LCD in Ungentum leniens ("cool cream") as useful steroid-sparing, antiinflammatory, antipruritic agents.

Patients may complain about the use of coal tar, especially crude coal tar, because of its strong odor and staining properties. To reduce the odor side effect, we add 3% menthol to LCD ointment. The main adverse effects are local irritation, burning, contact dermatitis, phototoxicity, and folliculitis.[105,109,110] Carcinogenicity is another concern because epidemiologic studies have linked polycyclic aromatic hydrocarbons to the development of cancer.[110,111] However, several publications, including the largest study of 13,200 patients, showed no increased risk of skin- or non-skin cancers using dermatologic coal tar.[112–113] Overall, coal tar remains a generally accepted treatment option for AD.[102,114]

Antipruritic Topicals

Menthol

Menthol is a naturally occurring cyclic terpene alcohol of plant origin that elicits a cooling sensation when applied to the skin. It is approved in concentrations up to 16% by the FDA for over-the-counter external use as a gel, cream, ointment, or foam and is often used as an antipruritic agent.[115] Menthol acts on the TRPM8 channel, which is a thermally sensitive receptor to innoxious cold.[116] The antipruritic mechanism of menthol is unclear, but theories include an activation of TRPM8 on C-fibers, direct stimulation of A-delta fibers,[117] and activation of κ-opioid receptors[118] Interestingly, cooling skin in a waterbath has been shown to reduce itch in AD patients[119]; therefore, the cooling sensation of menthol via TRPM8 or other mechanisms may be the antipruritic mechanism.[115] Although an effect of menthol via TRPM8 is likely, direct evidence in human skin and diseases is still lacking. Furthermore, agonists with an improved bioavailability and penetration profile may be better than menthol or camphor.[120]

Evidence regarding the efficacy of menthol is minimal, with two contradicting studies regarding menthol's effect on histamine-induced itch. In a study of 35 children, investigators reported improvement in itch from baseline after seven days of using a sprayable menthol product.[121] Side effects of menthol include allergic contact dermatitis,[122] and greater concentrations of 40% have resulted in erythema and burning.[123] In general, well-performed studies with optimized concentrations, thorough disease-adapted compounding, and large cohorts are still lacking. Although menthol appears to be a fairly safe product, it has been shown to lead to more transepidermal water loss than alcohol, so it should not be used as a substitute for an emollient.[124]

Capsaicin

Capsaicin, naturally occurring alkaloid from hot chili peppers, induces neurogenic inflammation[125] and has been reported as a treatment option against pruritus of various etiologies.[126–128] Capsaicin binds to the TRPV1 ion channel, which is a crucial receptor in the pain pathway.[23] TRPV1 is present on many C-fibers, and its activation leads to the release of neuropeptides (e.g., SP, CGRP).[129] The mechanism underlying the suppression of the itch sensation is thought to be the depletion and/or desensitization of $TRPV1^+$ C fibers.[130] The authors of a noncontrolled study evaluated 33 patients with prurigo nodularis (four of whom had underlying AD) and reported that a topical capsaicin ointment resulted in complete elimination of pruritus in all patients after 12 days.[128] The main side effects reported were burning, erythema, and increased itch. A meta-analysis and systemic review of capsaicin both question its overall efficacy in the treatment of pruritus in its current form.[131,132] However, according to our experience, many patients respond to topical capsaicin treatment in recalcitrant itch if other treatments fail. Should treatment with topical capsaicin be desired, we recommend starting with capsaicin at 0.025% and gradually increasing the dosage as needed. In sensitive areas, treatment with 0.006% may be effective as a starting concentration. Capsaicin should be applied 4–5 times per day for maximal efficacy. To enhance patient compliance, capsaicin may be combined with lidocaine gel, which should be applied 20 minutes before capsaicin application.

Topical Antihistamines

Although oral antihistamines (see section "Systemic Antipruritic Agents" in the article) are commonplace in the management of AD, topical antihistamines typically are used less frequently. Doxepin, a tricyclic antidepressant with antihistaminic effects, is available as a 5% cream and is approved by the FDA for up to eight days for the management of moderate pruritus in adult patients with AD. A double-blind, vehicle-controlled trial with 270 patients

showed relief of pruritus in 85% of doxepin-treated patients (applied four times daily) as compared with 57% of vehicle-treated patients by day seven.[133] When topical doxepin was combined with 2.5% hydrocortisone or 0.1% triamcinolone, it resulted in faster and greater relief of itching than either corticosteroid alone.[134] The authors of the studies on doxepin have been criticized for not demonstrating a significant clinical benefit and for having a study period of only one week.[135] The most common side effects were drowsiness, localized stinging, and burning. Other less-common side effects reported include dry mouth, pruritus, and exacerbation of eczema.[133,135] Several cases have been reported of allergic contact dermatitis to doxepin cream, most of which were patch test positive and in patients using it for more than eight days.[136] Evidence is lacking for other topical antihistamines such as diphenhydramine.[137] In our opinion, doxepin cream is a second- or third-line topical treatment for pruritus in AD, and other topical antihistamines should not be recommended.

Topical Naltrexone

The use of oral μ-opiate receptor (MOR) antagonists such as naltrexone is discussed in further detail in the section "Systemic Therapies." Topical naltrexone has been studied in patients with AD, with some patients showing decreased MOR in skin biopsies. Topical naltrexone demonstrated a 29.4% better effect on pruritus and faster time to relief than placebo.[138] More extensive clinical trials are necessary to clarify the benefit of topical naltrexone as an antipruritic agent.

Topical *N*-palmitoylethanolamine (PEA)

Cannabinoid-receptor activation is known to deescalate sensations of pruritus and pain.[139,140] N-palmitoylethanolamine (PEA) belongs to the family of the N-acylethanolamines which includes endocannabionoids such as N-arachidonoyl-ethanolamine (AEA). PEA has been found to have anti-inflammatory and analgesic effects; postulated mechanisms include downregulation of mast-cell degranulation[141] and enhancement of the anti-inflammatory effects exerted by AEA.[142] In a multinational, multicenter, observational, non-controlled, prospective cohort study of 2456 patients, investigators assessed the effect of a cream containing 0.3% PEA to improve the symptoms (dryness, excoriation, lichenification, scaling, erythema, pruritus) of mild-to-moderate AD.[143] Regular use of the PEA cream resulted in a reduction of pruritus on visual analogue scales from 4.9 to 2.7 at six days after start of treatment to 2.0 at the end of the observation period (4–6 weeks). In 1% of the total study population, side effects were causally related to the active compound in the study cream. The most common side effects were pruritus, burning, and erythema. The study lacked a control group, so future double-blind, vehicle-controlled trials are needed to determine the true efficacy and safety of PEA creams.

Systemic Therapies

Like the topical therapies described previously, systemic therapies of pruritus in AD are generally either directed at suppressing the underlying inflammation or targeting peripheral or central itch pathways. Examples of systemic anti-inflammatory agents include glucocorticoids, cyclosporine, azathioprine, methotrexate, and infliximab. Other medications against itch that are not directly anti-inflammatory include antihistamines and neuromodulators, including opioid receptor antagonists or agonists. The use of systemic antibiotics was discussed previously under the section on trigger factors. Except for antihistamines, because of their greater side effect profile, systemic medication is generally a second- or third-line treatment in AD when optimal topical therapy and phototherapy fail or are contraindicated. However, because pruritus has a dramatic impact on the quality of life in these patients, systemic therapies and early treatment can have an important role in AD management.

Systemic Antiinflammatory Agents

Systemic GCs

Antiinflammatory, immunomodulating therapies help to improve pruritus in AD by suppressing the underlying inflammatory mechanisms leading to itch.[144] Corticosteroids have many antiinflammatory effects, including blockage of the release of cytokines by T lymphocytes, which is likely the mechanism of the immediate diminishing of itch during treatment.[145] Only 2 randomized controlled trials evaluated the efficacy of systemic GCs, according to a systematic review.[146] One of them demonstrated that four weeks of oral beclometasone plus nasal beclometasone resulted in significantly decreased daily itch as compared with the use of placebo in children with severe AD.[147] The second study demonstrated that two weeks of systemic flunisolide in children with severe AD led to a significant reduction in pruritus as compared with the use of placebo.[148] Although oral corticosteroids are potent antiinflammatory agents, they are not routinely recommended because of significant adverse effects (e.g., suppression of the hypothalamic-pituitary-adrenal axis).[149] In addition, the recent development of many classes of effective topical GCs and improved derivatives of GCs with similar efficacy and fewer side effects argue against the need for regular use of systemic GCs in AD.

Cyclosporine A (CyA)

CyA is an immunosuppressant that can be used off-label for the treatment of AD. CyA binds to the intracellular receptor cyclophilin, leading to decreased T-lymphocyte activation and transcription of interleukin-2, which is an activator of pruritus.[150] Darsow et al[151] used CyA (5 mg/kg/d) for 10 days in 10 adults and demonstrated a significant decrease in itch intensity and total number of blood eosinophils over placebo; however, pruritus recurred immediately after therapy was discontinued. The authors of other studies have also reported the efficacy of CyA for the treatment of AD and associated pruritus in adults and children.[152–154] The authors of a meta-analysis found that the estimated mean clinical improvement in disease severity after 6–8 weeks of treatment was 55%, but after discontinuation, 50% of patients relapsed within two weeks.[155] The most common side effects of CyA are hypertension, renal dysfunction, headache, hypertrichosis, gingival hyperplasia, and paresthesias.[156] Other potential complications include hyperlipidemia, rebound flare after discontinuation, gout and, rarely, serious infections and malignancies.[135]

Other Systemic Immunomodulators

Other immunomodulators that have been studied for their potential use in AD include azathioprine,[157] methotrexate,[158] mycophenolate mofetil,[159] infliximab,[160] and interferon gamma.[161] Other review articles explore the role of these medications for the treatment of itch in further detail.[162,163] In reports, tumor necrosis factor-a blockers have been described as either minimally effective[164] or as even leading to AD-like eruptions.[165] The effectiveness of blockers of pathways involved in AD pathophysiology, such as immunoglobulin E (IgE; omalizumab),[166] IL-5 (mepolizumab),[167] and CD20 (rituximab)[168] is low. Recent efforts have also been made to test the efficacy of extracorporeal photochemotherapy[169] or immunoabsorption of IgE in AD.[170] The benefit of these methods for severe forms of AD have to await further study and optimization of treatment regimen.

Systemic Antipruritic Agents

Antihistamines

Although histamine has been long-established as a mediator of pruritus,[171] it is not considered a major mediator of pruritus in AD.[172] Studies have shown that AD patients had reduced itch sensations with intracutaneously injected or iontophoretically applied histamine

when compared with healthy subjects.[173,174] Therefore, it is no surprise that oral nonsedating antihistamines are not very effective against itch in AD. An evidence-based review of multiple randomized, placebo-controlled trials reported little objective evidence for an antipruritic effect of antihistamines in AD.[175] Anecdotally, sedating antihistamines may be more useful for their soporific effect and thus reduce scratching at bedtime, thereby generating less eczema.[149]

Opioid Receptor Modulators

Opioids activate spinal μ-, κ-, and δ-opioid receptors, leading to analgesia, but they often also evoke or intensify pruritus.[176–178] The effects of opioids can be reversed through antagonists of MOR, which are receptors that are expressed in the epidermis[179] and dermis.[180] MOR antagonists include naltrexone and nalfamene, which have been tested in the treatment of AD pruritus with variable results.[181] In studies in which the authors used nalfamene (10–20 mg/d) in AD, one trial reported significant reduction in itch as compared with placebo,[182] whereas another reported no significant differences as compared with placebo.[183] A study on naltrexone (50 mg daily) showed variable results in improving itch in patients with AD, with a stronger effect in other diseases such as psoriasis, bullous pemphigoid, and cholestatic pruritus.[184] In a double-blind, placebo-controlled trial in AD patients, oral naltrexone use resulted in significantly decreased pruritus as compared to placebo after one or two weeks.[185] Because of the lack of clear controlled studies, MOR antagonists should be recommended as second- or third-line treatment.[181]

For dosing, some authors recommend starting at a lower dose (e.g., 10 mg for nalmefene and 25 mg/d for naltrexone) and titrating up every three to seven days to minimize adverse events.[186] The main side effects reported have been dizziness, fatigue, nausea, vomiting, diarrhea, headache, and cramps. Side effects were dose-dependent and generally limited to the first two weeks of treatment and depended on speed of titrating the drug and interaction with other drugs.[181] Tachyphylaxis has been reported between four weeks to nine months and can be managed by increasing the dose or interrupting administration for two to three weeks.[187] κ-opioid receptor agonists, such as butorphanol[188] and nalfurafine,[189] have the potential for pruritus reduction but have not yet been described in treatment of AD-associated pruritus. Nalfurafine has been approved in Japan as a treatment of renal itch. Further controlled studies are needed to evaluate the safety and efficacy of oral opioid receptor modulators, as a treatment option against pruritus in AD.

Neural Modulators

There are systemic medications that target itch through a direct interaction with nerves and neurotransmitters. Such agents (eg, gabapentin, pregabalin, amitriptyline, mirtazapine, and paroxetine) are described elsewhere in this issue (See "Pruritus: Management Algorithms and Experimental Therapies" in this issue, Steinhoff and Berger 2011). There is report of mirtazapine improving nocturnal itch in patients with AD.[190] A study evaluating paroxetine or fluvoxamine for the treatment of chronic pruritus reported considerable reduction in pruritus in three patients with AD.[191] Because there are no randomized controlled trials at this time for the use of these medications in AD, they should be used cautiously. Aprepitant (Emend®), which is approved by the FDA as an antiemetic drug, suppresses itch by antagonizing the stimulatory effect of SP on the neurokinin-1 receptor in the peripheral skin, nerve endings, and probably brain.[6,192] So far, the effectiveness of aprepitant as an antipruritic has been described in Sezary syndrome[193] and prurigo nodularis.[192] The role of aprepitant in AD therapy is still unclear.

Phototherapy

Phototherapy is a useful therapeutic option for AD and pruritus.[194] It allows for effective treatment (especially for generalized disease), with good systemic safety. The wavelengths and types of phototherapy available include ultraviolet B (UVB), ultraviolet a (UVA), ultraviolet A1 (UVA1), combined UVA/B, and psoralen plus UVA (PUVA). Various mechanisms of action have been proposed for phototherapy. One potential explanation for the efficacy of phototherapy on pruritus is through reduction of nerve fibers in the epidermis.[195] In addition, high-dose UVA1 has been shown to decrease IgE-binding and mast cell numbers in the dermis and inhibit Langerhans cell migration out of the epidermis.[196] UVA/B combination therapy has been shown to decrease the number of HLA-DR+ T cells in AD patients.[197]

Various studies have documented the efficacy of UVB (290–320 nm),[198] NB–UVB (311–313 nm),[199] UVA/B combination,[200] and UVA(1)[201] therapy for improving the severity of AD, including the associated pruritus. In an early study of phototherapy, patients reported better pruritus scores for the half of their body that was treated with UVB than for the half treated with placebo.[198] A later study showed that 90% of patients receiving NB–UVB reported a reduction in itch as compared to 63% receiving UVA and 52% receiving visible light (placebo). In that study, patients were allowed to use moderate-to-potent topical corticosteroids during the treatment period, which is likely why the placebo group had such a high response rate.[202] UVA1 is another phototherapy option for AD, although it is less commonly available than UVB. High-dose UVA1 is more effective than fluocortolone therapy in reducing the severity of AD (pruritus was included in the scoring system).[203]

Systemic PUVA has been shown to be effective in AD.[204,205] One study reported that before skin lesions resolved, pruritis was always relieved, usually in the first two weeks of treatment.[206]

The excimer 308-nm laser is a new option in ultraviolet phototherapy and has shown efficacy in the treatment of AD. Studies demonstrated an 81% reduction in baseline itching scores after one month of twice weekly treatments.[207,208] The excimer laser also appears equivalent to clobetasol propionate, 0.05% ointment in average improvement of pruritus in the prurigoform of AD.[209]

The combination of crude coal tar with phototherapy, also referred to as "Goeckerman therapy," was first described by William Goeckerman in 1925.[210] Since then, the Goeckerman therapy regimen has been used with good safety and efficacy in children and adults with severe, generalized AD. In our experience, most of our patients report a dramatic improvement in pruritus after completion of therapy. Publications on the efficacy of Goeckerman therapy have been focused on psoriasis patients,[211,212] but its usefulness for patients with pruritic AD should not be forgotten.

Phototherapy is generally considered a relatively safe treatment for adults and children, especially in patients with generalized disease who would potentially require systemic medications. The most common side effects of UVB therapy are erythema and tanning. Aging of the skin can be seen with UVA and UVB therapies. Side effects of PUVA include erythema, burning, pain, itching, headache, and nausea. Other side effects include PUVA lentigenes.[194] Side effects of the excimer 308-nm laser included burning, erythema, pruritus, hyperpigmentation, and more rarely, vesicles, edema, and generalized exacerbation.[207]

One of the main concerns regarding phototherapy is its potential carcinogenic effect. In general, UVB is considered to have no risk or a slightly increased risk of nonmelanoma skin cancers.[213–216] With PUVA, there appears to be a risk of non-melanoma skin cancer

(especially squamous cell carcinoma),[217–219] and the association of PUVA and melanoma remains controversial.[220,221]

Overall, phototherapy in its variety of forms has demonstrated efficacy as a treatment for AD and its associated pruritus. Phototherapy can be useful alone or in combination with other therapies, and can serve as a safe first- or second-line treatment, especially for patients who have wide-spread or generalized disease and/or cannot tolerate other systemic therapies.

Lidocaine

The efficacy of systemic lidocaine (a sodium channel blocker, amide local anesthetic and antiarrhythmic drug) for alleviating acute or chronic pain was discovered 50 years ago.[222,223] Subsequently, the use of intravenous lidocaine was also a successful therapeutic intervention for managing intractable neuropathic pain syndromes.[224] However, although the effectiveness of lidocaine to relieve neurogenic diseases is established, only a few case reports recognize the potency of lidocaine to attenuate neuropathic pruritus.[225–227] The authors of one larger, early observational, uncontrolled study from 1961 investigated the effect of a topically applied lidocaine containing "Lida-Mantle Cream" on 50 patients with pruritic dermatologic disorders, among which is the only patient with AD reported to have been treated with topical lidocaine to our knowledge.[228] In that patient, the relief from pruritus was classified as excellent. Of note, a recent study on scratch behavior in mice does point to a strong inhibitory effect of lidocaine on itch.[229] This and the few existing case reports on the alleviating effect of lidocaine on neuropathic itch lead us to hypothesize that lidocaine might be beneficial for patients with AD. To prove this hypothesis, further basic research and controlled studies are needed to evaluate the safety and efficacy of lidocaine in the treatment of pruritus in AD.

Complementary and Alternative Treatments

Although traditional Chinese herbal therapy (TCHT) is usually prescribed for an individual, standardized formulations have been studied in randomized controlled trials for the treatment of itch. A double-blind, placebo-controlled trial of a TCHT concoction consisting of 10 herbs in adults with AD reported decreased itching and improved sleep quality as compared with placebo.[230] Adverse effects reported related to this 10-herb mixture include dizziness, nausea, mild abdominal distention, and headache.[231] A proposed mechanism of action of the anti-inflammatory and antipruritic effect of the herbal mixture includes an inhibitory effect on CD23 expression in peripheral blood monocytes.[232]

In a more recent randomized, placebo-controlled study of THCT, authors evaluated Xiao-Feng-San, an herbal preparation of 12 herbs, in patients with AD. Patients who received Xiao-Feng-San demonstrated significant improvement on their clinical lesion score, erythema score, and self-reported sleep and pruritus score as compared with placebo. The main adverse effects reported were abdominal pain and dyspepsia.[233]

Individual botanicals that may have possible benefit for AD[234] include St John's wort,[235] licorice,[236] and mahonia.[237] Other complementary therapies that have been studied in AD include hypnotherapy,[238] biofeedback,[239] and massage therapy.[239] A small noncontrolled study on hypnotherapy in children with severe, therapy-resistant AD reported that 10 of 12 patients experienced a significant improvement of their itch and scratching 18 months after treatment.[240] In general, there is little controlled evidence for the efficacy of complementary and alternative treatments, so further larger randomized controlled studies are required for adequate interpretation of efficacy.

Psychological Intervention

Psycho-emotional stress, both acute and chronic, and other psychological factors such as depression exacerbate itch in patients with AD.[241,242] As patients become more pruritic, they scratch more, which in turn worsens their dermatitis and leads to more itch.[243] The vicious itch-scratch cycle then perpetuates a high state of anxiety and stress.[244] Furthermore, uncontrolled AD and itching can eventually progress to psychosocial morbidity.[245] The mechanism of stress-induced pruritus in AD patients is not clear, although some theories suggest that enhanced anxiety leads to increased expression levels of nerve growth factor and the release of neuropeptide Y,[246] increased pruritogenic mediators from mast cells,[247] and increased levels of IgE, eosinophils, interferon-γ, and interleukin-4.[248] Autonomic nervous system dysfunction may also play a role.[249] Therefore, supporting patients to learn to manage their stress and resultant scratching behavior may lead to disease improvement and better prevention of relapses.

Psychological interventions used in AD often focus on body relaxation and maintaining control over the desire to scratch when one feels itchy. A study that evaluated a stress management group program based on the ABC model (awareness, balance, and control) as compared with control showed no significant difference in eczema severity but did show an improvement in itching intensity.[250] A randomized controlled trial showed that AD patients receiving cognitive-behavioral treatment, autogenic training as a form of relaxation therapy, or combined education and cognitive-behavioral treatment demonstrated significantly decreased itching intensity and scratching behavior after one year, as compared to those receiving only standard dermatologic care.[251] The study also reported that the psychological intervention groups used less topical steroids than the standard dermatologic care group.

Habit reversal is another psychological approach to manage pruritus. Because scratching in patients with AD can become a conditioned response,[252] it may be helpful to target the scratching behavior. The habit reversal technique teaches patients to recognize the habit of scratching, identify situations that provoke scratching, and train them to develop a competing response practice (eg, clenching fists).[253] Two studies have demonstrated that topical corticosteroids combined with habit-reversal treatment led to a significant reduction of scratching episodes per day as compared to topical steroids alone.[254,255]

One of the additional benefits of psychological approaches is that adverse events are essentially nonexistent. Overall, a meta-analysis of these various psychological techniques suggested that there is a role for such interventions in the management of AD and associated pruritus. The most effective psychological intervention for AD appears to be a combination of stress-managing psychotherapy, relaxation techniques, and habit reversal behavioral therapy.[256]

Combination Therapy

Because itch in AD is multifactorial, combining therapies can be a useful approach to management. In general, elimination of trigger factors and psychological/behavioral interventions can be combined with any other therapies. Emollients are safe in combination, but should be used with care with phototherapy because they may affect the transmission of UV.[257] Phototherapy is generally not recommended in combination with topical calcineurin inhibitors and certain oral immunosuppressants (eg, methotrexate) because of the theoretic risk of increased malignancy.[258] Medications with similar mechanisms of action or side effects should typically be avoided (eg, topical doxepin with oral antihistamines or azathioprine with methotrexate). Used with caution, a combination therapy can help to manage severe itch in AD that is otherwise uncontrolled by monotherapy.

Patient Education

The variety of therapeutic options discussed are useful only if the patient and/or people assisting the patient understand how to use the treatment and are willing to adhere to the recommended regimen. This is especially relevant in chronic diseases like AD. Examples of barriers to treatment include misunderstanding of treatment instructions, forgetting to use the medication, disliking the formulation or side effects of the medication, and fearing adverse effects.[259,260] Because many of these barriers can be addressed through patient education, physicians and other health care providers should strive to incorporate education into their patient management.

Key components to successful communication are to spend time explaining the nature of the disease and medications being prescribed, to use practical demonstrations of medication application when appropriate, and to use written and verbal instructions.[261,262] Even discussing adherence with patients can lead to improved medical results.[263] An uncontrolled study of 51 children with AD reported that repeated education and demonstration of topical therapies by a dermatology nurse led to an 800% increase in the use of emollients, 89% reduction in the severity of eczema, and an 85% reduction in the severity of pruritus.[261] A written action plan for eczema (mirroring the use in asthma) is becoming a more widely used education tool, and may be helpful in increasing patient understanding and adherence.[264,265] Visual aids and pictures are effective for patients[266] and may be more effective than text alone.[267] Medication visual aids, such as one designed by the first author (Fig. 1), may help optimize compliance and therapeutic success. Regardless of the type of approach or tools used, patient education should be a part of the management of AD.

Multidisciplinary Approaches

Because optimal management of AD patients requires the use of medication and therapeutics, patient education, and psychosocial interventions and support, multidisciplinary AD programs have been developed at various institutions. They combine various health care experts to cover different aspects of living with the disease, including managing itch.

A nursing program called "Coping with Itch" that was developed at the University Medical Center Utrecht in the Netherlands combines patient education, individual counseling, cognitive behavioral therapy, and referrals to social workers or psychologists as needed. A randomized controlled study showed no clear significant difference ($P = 0.07$) in regards to frequency of itching and scratching between the intervention and control group, but there was a significant difference in catastrophizing and helpless itch-related coping.[268] Both catastrophizing and helpless coping have been shown to be predictors of psychosocial morbidity.[269]

Another program with educational and psychological intervention was from the Radboud University Nijmegen Medical Center, also in the Netherlands, and consisted of group sessions with a psychologist/cognitive behavior therapist and dermatology nurse specialist, along with daily homework assignments from a booklet. Compared with the control "waiting list" group, the intervention group showed significant improvements in itch, scratching behavior, itch-coping patterns, and skin severity, not only immediately after treatment, but also three and 12 months after treatment completion. This reflects the potential long-lasting impact of such psychoeducational programs.[270]

A study from seven hospitals in Germany showed that a multidisciplinary education program for children with AD improved itching behavior, specifically the subscales of catastrophizing and coping in 8- to 12-year-old patients and catastrophizing in 13- to 18-

year-old patients. The program consisted of six, once weekly sessions carried out by dermatologists or pediatricians, psychologists, and dieticians.[271]

In the United States, the National Jewish Medical and Research Center in Denver, CO has the Atopic Dermatitis Program, which involves a multidisciplinary team that includes allergist-immunologists, psychologists, nurse educators, child life specialists, and dietitians. The program has educational components (e.g., group sessions, written materials, action plans) and psychological components (e.g., cognitive therapy, biofeedback, art therapy).[272] The program has reported sustained improvements in symptoms of AD in 50 children older than two years of age.[273]

Although more randomized controlled studies are needed to further evaluate the efficacy of a multidisciplinary approach to AD and itch, the current reports are very promising. For complex chronic diseases, such as AD, there is a dynamic interplay between biological, psychological, and social factors. A multidisciplinary approach seems not only appropriate, but also necessary.

Summary and Conclusions

Improving and controlling itch in AD requires attention to various aspects ranging from elimination of trigger factors, adequate stage-adapted topical or systemic therapy, to psychological intervention. Dermatologists have a "toolbox" of therapies for targeting pruritus in AD (Table 2). These can be topical medications, systemic drugs, or phototherapy, with mechanism of actions that are antiinflammatory and/or anti-pruritic with little direct effect on inflammation. Psychological and behavioral interventions are also useful for helping AD patients manage their itch. Regardless of what treatments or medications are prescribed, education is a fundamental component to caring for AD patients. Some centers have begun to implement multidisciplinary clinics with physicians, nurses, psychologists, social workers, and other health care providers as a way to address the multifaceted aspects in the life of patients with AD and pruritus. The management of pruritus in AD can be a complex process, but with proper application of therapeutic options, effective education and communication, and long-term perseverance, one can help AD patients achieve control of their itch.

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Figure 1.
Visual aid for patient medication in children.

Table 1

Therapeutic Ladder for AD Associated Pruritus

Treatment Category	First Line	Second Line (or First Line in Severe Disease)	For Consideration but Controversial and/or Minimal Evidence
Trigger elimination	• Avoiding exogenous triggers (see Table 2) • Antimicrobials for overt secondary infection • Stress management	• Food allergen avoidance in symptomatic patients	• Bacterial decolonization • Food allergen avoidance in asymptomatic patients • Dust-mite reduction
Topical therapy	• Emollients • Corticosteroids	• Calcineurin inhibitors * • Coal tar	• Menthol • Capsaicin • Naltrexone • Doxepin
Systemic therapy		• Oral sedating antihistamines (minimal evidence in AD, but soporific effect may be helpful) • Combination of nonsedating and sedating antihistamines (high-dose) • Cyclosporine A • Corticosteroids	• Other immunosuppressants (eg, azathioprine, mycophenolate mofetil, methotrexate, interferon-gamma) • Mu-opiate receptor antagonists • Kappa-opioid agonist • Neurogenic agents (eg, gabapentin, mirtazapine, paroxetine)
Other	• Education about disease and treatment modalities • Written instructions and/or handouts in addition to verbal instructions	• Phototherapy (UVA, UVA1, UVB, Combination, PUVA) • Goeckerman (phototherapy + tar) • Psychological interventions (eg, cognitive-behavioral therapy, habit reversal therapy, autogenic training)	• Excimer laser • Herbals and botanicals • Hypnotherapy • Massage • Biofeedback • Acupuncture

AD, atopic dermatitis.

*
May be also used as first line for maintenance therapy.

Table 2

Trigger Factors in AD for Consideration in the Long-Term Management of AD

Allergies	House dust mites, food allergens, air-born contact dermatitis (pollen, etc), animals, jewelry.
Infections	*Staphylococcus aureus*, viral infections (herpes, molluscum), yeasts (eg, *Trichophyton*, malassezia).
Exogenous	Soaps, solvents, wool, sweat, chemicals, toxins, cigarette smog, certain ingredients of cosmetics
Physical stimuli	Temperature: humidity, cold dry air, clothes (alloknesis)
Emotional	Anxiety/stress

AD, atopic dermatitis.