

Chapter 13

Atopic Dermatitis: Managing the Itch

William S. Farmer and Kalyani S. Marathe

Abstract Atopic dermatitis has a substantial impact on sleep, appearance, psychological well-being, and other qualities of life. The visual appearance of lichenification, cheilitis, hyperpigmentation, ichthyosis, and erythema can be socially stigmatizing, and treatment of these symptoms is challenging. In managing pruritus in patients, practitioners should assess and document pruritus through questionnaires at each routine visit. Initially, practitioners should advise patients to employ non-pharmaceutical treatments such as emollients with wet wraps, elimination of triggers, changing scratching habits, and psychological interventions. If these methods of treatment are not successful or if the disease presentation is severe, pharmacological therapies should be employed. This chapter describes the therapeutic ladder for pruritus in atopic dermatitis and discusses each treatment modality in further detail for practitioners to advise their patients.

First-line topical pharmaceutical agents include topical glucocorticoids and topical calcineurin inhibitors. Second-line topical agents include coal tar, menthol, capsaicin, or doxepin. After the use of topical agents has been exhausted, primary systemic agents can be applied. These include sedating antihistamines, non-sedating antihistamines, oral glucocorticoids, or cyclosporine A. Finally, neuromodulating or immunomodulating agents can be attempted, including SSRI/SNRIs, TCAs, immunosuppressants, neural modulators, and opioid receptor modulators. Outside of pharmacological treatments, phototherapy has been shown to provide a dramatic improvement of pruritus in atopic dermatitis and can be used at any stage of treatment including as a first-line agent.

Keywords Pruritus • Treatment • Anti-Pruritus therapeutic ladder

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13.1 Introduction

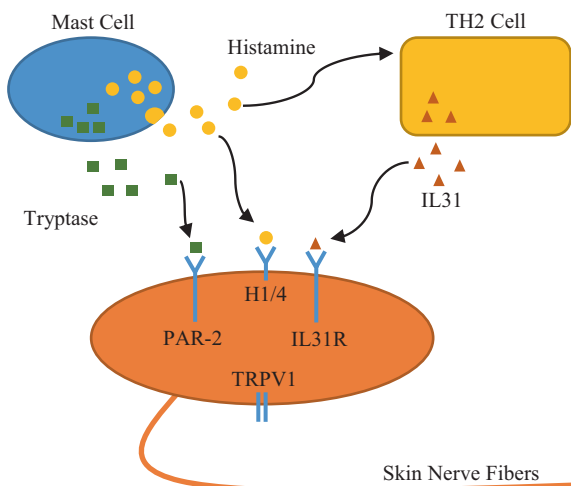
Atopic dermatitis is referred to as “the itch that rashes” due to the extensive pruritus involved in the disease [1]. The disease has a significant impact on major aspects of quality of life including sleep, appearance, and psychological well-being. Nocturnal pruritus often hinders sleep which causes anxiety and daytime somnolence. The visual appearance of lichenification, cheilitis, hyperpigmentation, ichthyosis, and erythema can be socially stigmatizing. Social isolation and embarrassment can occur in children as well as adults. The disease impacts care takers, demanding money, time, and energy. While the pathophysiology of pruritus in atopic dermatitis is incompletely characterized, some molecular mechanisms are known to play a role, as demonstrated in Fig. 13.1. These mechanisms include: histamine 1/4 receptors (H1R, H4R), protease-activated receptor 2 (PAR 2), interleukin 31 receptor (IL31R), and transient receptor potential cation channel subfamily V member 1 (TRPV1).

13.2 Pathophysiology of Pruritus

Complement and immunoglobulin deposits have been discovered in patients with atopic dermatitis within the dermal-epidermal junctions [2]. The highest density of thin, unmyelinated C-fibers that mediate pruritus are located in this same junction [3, 4]. For this reason, patients may scratch their skin until it bleeds because erosion of the dermal-epidermal junction is thought to provide relief [5].

Histamine is also thought to play a role in the development of itch. Basophils and mast cells release histamine which binds to central and peripheral receptors. Histamine is an autocasoid that has been found to be increased in atopic dermatitis

Fig. 13.1 Proposed pathophysiology of pruritus in atopic dermatitis with H1/4, PAR-2, IL31R, and TRPV1



lesions [5, 6]. The histamine 4 receptor specifically has been shown to play a role in atopic dermatitis pruritus and is believed to be activated on Th2 cells leading to IL-31 production [5–9]. Although studies suggest a role of both H1R and H4R in pruritus, only H1R antagonists are available to treat pruritus [5]. Within the class of H1R antagonists, efficacy of non-sedating antihistamines has been limited in the treatment of atopic dermatitis, suggesting the lack of a significant role of peripheral histamine 1 receptors for atopic dermatitis [9]. In addition to histamine, mast cells are thought to release tryptase which binds to specific receptors on nociceptive afferent nerves known as PAR-2 [10]. Atopic dermatitis lesions have been found to demonstrate enhanced immunostaining for PAR-2. Thus, another proposed mediator for atopic dermatitis pruritus is PAR-2.

Several therapies for pruritus in atopic dermatitis utilize transient receptor potential (TRPV1) ion channels on C fibers which activate pain neurons. These ion channels respond to heat and cold temperatures, to protons via pH changes, and to biological mediators such as prostanoids. It is thought that phosphorylation and desensitization of these ion channels work to counteract pruritus.

13.3 Assessment of Severity of Pruritus

Assessment of the severity of the pruritus is important so that improvement can be monitored over time. Particular features of the disease are important to characterize: the severity of the excoriations, distribution of the pruritus, lesion morphology, presence of alloknesis (itch produced by gentle touch), color, history of skin infections, presence of urticaria, intensity of the pruritus, duration, frequency, location, and quality of the pruritus, aggravating and palliative factors, current treatments, quality of life, degree of disability, coping strategies, and scratch response. Other medical history components are important as well: patient age, current medications, presence of diabetes or malignancy, triggers (heat, cold, change in weather, water, chemicals, haptens). These features allow the practitioner to assess the severity of the pruritus to help determine what type of treatment would be best suited for the patient. Symptoms concerning for systemic involvement that should be investigated include: anemia, cholestasis, immunosuppression, infections, jaundice, presence of other skin diagnoses, signs of neoplasia, signs of psychiatric disease, and weight loss [11]. The presence of these factors may be cause for a more comprehensive workup with blood testing, including: a complete blood count, ferritin, folates, total iron binding capacity with iron, reticulocyte count, vitamin B12, folic acid, and liver function tests.

Because pruritus can be subjective, a questionnaire can be used to determine the severity of the pruritus at each office visit. Table 13.1 lists assessment question topics to document pruritus in patients. The Eppendorf Itch Questionnaire, shown in Fig. 13.2, is a short survey that rates the severity of the symptoms and assesses the temporal nature of the pruritus, location of the itch, and palliation [12]. It is helpful in assessing a patient's symptoms in a more objective manner.

13.4 Interventions

Identification and elimination of pruritic triggers can improve quality of life in patients with atopic dermatitis. Patients should be educated on possible triggers so that they can keep track of potential exposures. Common factors that can induce pruritus include: animals, cigarette smoke, cosmetics, detergents, dry air, wool clothing, dust mites, food allergens, humidity, jewelry, long and hot baths/showers, non-cotton clothing, pollen, polyester, and sweat. Infections including *Staphylococcus aureus*, Herpes simplex, *Trichophyton* species, and *Malassezia (pityrosporum)* can also trigger pruritus. Emotional stress has been known to trigger pruritus as well [13].

Patients should be advised to wear 100% cotton clothing. Silver-based textiles have been produced for additional clothing options outside of cotton due to their antiseptic nature, suppressing *S. aureus* colonization & toxin formation [14]. Patients should bathe regularly with fragrance-free detergents. The patient should be advised to avoid smoking and second-hand smoke exposure. Ideally, patients should keep their homes clean and free of dust, mold, and pollen to minimize allergen exposure. Humidifiers and dehumidifiers can be purchased to improve air quality; however, these should be thoroughly cleaned regularly to prevent microorganism contamination.

13.5 Non-pharmacological Interventions for Pruritus

Patients can perform certain measures to minimize pruritus and skin damage from excoriations. These nonpharmacological interventions for pruritus are listed in Table 13.2. Cutting fingernails and keeping them well-filed can minimize trauma caused by excoriation. If tolerated, wearing soft cotton gloves at night can be especially helpful for younger patients. Practitioners should advise skin rubbing and cooling rather than scratching. Soaking the skin in a cool water bath has been found

Table 13.2 Nonpharmacological interventions for pruritus

Chinese herbal therapy
Cool water baths
Cutting fingernails
Elimination of triggers
Emollients
Psychological coping strategies
Rubbing & cooling
Tepid water baths
Wearing gloves at night
Wet wraps

to reduce pruritus in patients with atopic dermatitis [13]; moreover, tepid baths may also be helpful to alleviate pruritus. Bathing should be immediately followed by use of bland emollients such as fragrance-free ointments and humectants.

Wet wraps are a commonly used therapy for controlling active eczema and associated pruritus. The practitioner should instruct the patient to apply warm wet cotton bandages over the lesion and then to apply a dry dressing over top. Not only can this reduce pruritus, but it can also alleviate erythema and crusting. Covering skin lesions limit access to the skin preventing further excoriation especially at night. Emollients can be placed under the wet wraps to reduce symptoms. Topical medication placement under wet wraps should not be used as first line but can be used for unresponsive and recalcitrant lesions [13]. An alternative method of wet wrapping involves the use of generous bland ointments to moisturize the skin, followed by the application of petroleum jelly impregnated gauze, then covering with a dry rolled gauze dressing.

Traditional Chinese herbal therapy has been shown to have some success compared to placebo in reducing pruritus and improving sleep quality when compared to placebo in randomized controlled trials. Reported adverse effects include: dizziness, headache, abdominal distention, and nausea. It is thought that herbal remedies may have an inhibitory role in monocytes expression of CD23 [13]. St John's wort, licorice, mahonia, hypnotherapy, biofeedback, and massage therapy are other homeopathic therapies used to alleviate pruritus. There is insufficient evidence regarding published controlled trials on homeopathic remedies in atopic dermatitis [13].

Randomized controlled trials with patients receiving cognitive-behavioral treatment and relaxation therapy after 1 year have shown significantly decreased pruritus and scratching episodes when compared to standard dermatologic care. Not only do psychological factors exacerbate pruritus, but the itch-scratch cycle of atopic dermatitis causes anxiety. Specifically for managing pruritus, studies have demonstrated that habit reversal therapy alongside topical corticosteroids has shown significant reductions in scratching when compared with steroids alone [15]. Practitioners should assess and help manage patients' stress and anxiety at each appointment in order to prevent exacerbation of pruritus.

13.6 Topical Therapies for Pruritus

Once elimination of triggers, emollients, wet wraps, habit modification, psychological support, and other non-pharmacologic therapies have been tried, topical therapies should be initiated. Topical therapies may also be used for extensive lesions that are unlikely to respond without pharmacotherapy. Due to the risk of side effects, topical therapies should be tried prior to initiating systemic therapies. The vehicle of topical therapies should be heavily considered. For acute care, lotions, foams, and creams can be considered, although when applied to open or excoriated skin, these can cause burning and pain. For chronic care, ointments and ceramide-containing creams should be used. Based on the location of the lesion, particular

Table 13.3 Topical pharmacological interventions for pruritus in atopic dermatitis

Calcineurin Inhibitors	Pimecrolimus 1% cream; tacrolimus 0.03, 0.1% ointments	Transient burning, erythema, pruritus
Capsaicin	Start 0.025% cream 4–5× daily, gradually increase as needed up to 0.1%; 0.006% cream on sensitive skin	Burning, erythema, pruritus
Coal tar	20% coal tar + petrolatum (gold tar); 3–5% coal tar + unguentum leniens, (cool cream)	Burning, contact dermatitis, folliculitis, irritation, phototoxicity
Doxepin	5% cream	allergic contact dermatitis, burning, eczema exacerbation, and pruritus, somnolence, stinging, xerostomia
Glucocorticoids	Clobetasol propionate 0.05% lotion; desonide hydrogel 0.05%; fluticasone propionate 0.05% cream; hydrocortisone 1%; methylprednisolone aceponate 0.1% cream; prednicarbate 0.25% ointment	Adrenal suppression, chills, infection, skin atrophy
Lidocaine	3% cream; 5% patch	Erythema, edema, hypersensitivity
Menthol	1–3% cream increase up to 16%	Contact dermatitis
PEA	0.3% cream	Burning, erythema, pruritus

vehicles may be more ideal. Foams are an elegant vehicle for hair-bearing sites such as the scalp [11]. The main topical therapies used for pruritus that will be discussed are listed in Table 13.3 and include: coal tar, menthol, capsaicin, doxepin, naltrexone, PEA, and lidocaine. Topical corticosteroids and calcineurin inhibitors will be discussed in the chapter on atopic dermatitis management.

13.6.1 Coal Tar

The exact mechanism of coal tar is not understood; however, it has been shown to have antimicrobial, anti-inflammatory, and antipruritic effects. It comes in a variety of formulations which are often compounded with glucocorticoids. As an alternative to glucocorticoids, 20% coal tar can be compounded with petrolatum known as gold tar or 3–5% coal tar compounded with unguentum leniens can be used, which is known as cool cream. Three percent menthol is added to reduce odor [16]. There are few randomized controlled trials on coal tar for patients with atopic dermatitis, and it remains a second line agent. Reported trials have shown significant improvement with excoriation [13]. The main adverse effects of coal tar include burning, contact dermatitis, folliculitis, irritation, and phototoxicity [17]. Publications have shown no increased risk of cancers with topical coal tar [18].

13.6.2 Menthol

Menthol is a cyclic terpene alcohol antipruritic agent whose mechanism of action is not understood. It is thought to act on A-delta fibers, κ -opioid, and C-fiber TRPM8 channels that are thermally sensitive to cold temperatures [13]. Over the counter external use is approved up to 16% by the Food and Drug Administration as a cream, foam, gel, or ointment. Menthol is considered safe with the main adverse effect of menthol being contact dermatitis. It should be noted that because menthol can cause increased transepidermal water loss, it should not be substituted for emollient [19].

13.6.3 Capsaicin

Capsaicin is an alkaloid (8-methyl-N-vanillyl-6 nonenamide) made from hot chili peppers which induces neurogenic inflammation likely by depletion and desensitization of the transient receptor potential (TRPV1) ion channels C fiber [20]. These ion channels respond to physical and biological mediators such as heat, cold, pH changes, and prostanoids to counteract pruritus via activating pain neurons [11]. The stimulation of neuropeptide release that occurs upon applying capsaicin produces an intense burning sensation for usually half an hour; however, in most cases these symptoms resolve after 2–3 weeks. Although case-control studies are lacking and its overall efficacy has been questioned in systematic review for atopic dermatitis, there have been reports of topical capsaicin ointment in atopic dermatitis reducing pruritus within 12 days [21]. Adverse effects of capsaicin are burning, erythema, and pruritus. It is recommended to start at capsaicin 0.025% topical four to five times daily and gradually increase the dose as needed. The exception to this is sensitive skin areas such as face, axillae, or groin in which case 0.006% capsaicin should be used. Lidocaine gel, cream, or patch can be applied 20–60 min prior to capsaicin application to reduce burning and increase compliance [19].

13.6.4 Doxepin

Topical antihistamines are not considered effective for pruritus associated with atopic dermatitis; however, clinical trials have found that topical doxepin was the only anti-histamine with efficacy for chronic pruritus [11]. Doxepin is a tricyclic antidepressant with anti-adrenergic and anti-serotonergic properties as well as potent H1 and H2 blocking properties. Doxepin is a second or third line agent for atopic dermatitis and is approved by the Food and Drug Administration as a 5% cream for up to 8 days of treatment for adults [22]. Randomized controlled trials have shown a significant reduction in pruritus relief after a week of use compared to a vehicle [23]. Doxepin combined with 2.5% hydrocortisone or with 0.1% triamcinolone provided faster and greater pruritus relief than either corticosteroid alone

[24]. It is relatively safe with a long history of use; adverse effects of doxepin include allergic contact dermatitis, burning, eczema exacerbation, and pruritus, somnolence, stinging, and xerostomia [25]. Short duration of therapy limits use.

13.6.5 Topical N-Palmitoylethanolamine (PEA)

PEA (N-palmitoylethanolamine) is a cannabinoid agonist that has been shown to have analgesic and anti-inflammatory effects likely by downregulating mast cell degranulation. Activation of the cannabinoid receptor has been found to prevent pruritus from escalating [11]. PEA 0.3% cream has been found to improve pruritus and excoriation in patients with moderate atopic dermatitis [26]. One study that lacked a control group showed a 45% reduction in pruritus based on a visual analog scale after 6 days, and after 4–6 weeks there was a 60% scale reduction in pruritus. Due to lack of data, PEA is not commonly used for atopic dermatitis. Adverse effects include burning, erythema, and pruritus [13].

13.6.6 Lidocaine

Lidocaine is amide local anesthetic, anti-arrhythmic, and sodium channel blocker also used for the management of neuropathic pain. There are only a few studies showing topical lidocaine's effectiveness for pruritus; however, the anti-pruritic nature of lidocaine has been established in mice [13, 27].

13.6.7 Naltrexone

Some patients with atopic dermatitis have been shown to have biopsies with a decreased number of μ -opiate receptors in the skin. Opioid receptor modulators are more thoroughly discussed later in the systemic therapies for pruritus. In one study, topical naltrexone was found to have a 29.4% improvement on pruritus and faster time to relief than placebo [24]; however, naltrexone remains understudied for pruritus. For this reason, naltrexone is not commonly used as a first-line agent for pruritus.

13.7 Phototherapy

Ultraviolet A, ultraviolet A1, broad-band ultraviolet B, narrow-band ultraviolet B, psoralen ultraviolet light, and excimer 308-nm laser have been found to be effective in reducing pruritus in patients with atopic dermatitis. It is considered a safe first or second-line treatment, especially for wide-spread and generalized atopic dermatitis

and for those who do not tolerate other systemic therapies. Phototherapy is a good therapy for topical antihistamine and steroid resistant pruritus in pregnant patients. The exact mechanism of the direct role of ultraviolet therapy on cutaneous cell release of anti-pruritic mediators is not well understood. Several mechanisms of action have been proposed including: inhibition of pro-inflammatory mediators (IL-1 and tumor necrosis factor alpha), inhibition of anti-inflammatory neuropeptides release, inhibition of immunoglobulin E binding, reduction of mast cell numbers, inhibition of Langerhans cell epidermal migration, reduction of the number of HLADR+ T cells, and destruction of epidermal cutaneous nerves [11, 13]. Longer wavelengths of phototherapy penetrate farther into the skin. Ultraviolet A can reach the superficial to mid-dermis, whereas ultraviolet B remains in the epidermis. Because neurons associated with pruritus are thought to be at the dermal-epidermal junction, phototherapy applied deeper than the epidermis is more effective in reducing pruritus. Patients receiving high-dose ultraviolet A1, which is less commonly available than ultraviolet B, have been shown to be more effective than topical corticosteroids on reducing the severity of pruritus in patients with atopic dermatitis [28]. Combining oral psoralen with ultraviolet light therapy (pUVA) has been found to relieve all symptoms of pruritus within the first 2 weeks of treatment [29]. Twice weekly 308 nm laser UVB therapy has been shown to have an 81% reduction from baseline pruritus scores after 1 month [30]. Moreover, 308 nm laser has shown equivalence to clobetasol propionate 0.05% ointment for pruritus in atopic dermatitis [41]. Narrow-band ultraviolet B has shown success when combined with steroids/antihistamines or cyclosporine [11, 13]. The combination of phototherapy with crude coal tar is known as Goeckerman therapy, first described by William Goeckerman in 1925. While most studies have been limited to psoriasis, Goeckerman therapy is safely used for atopic dermatitis in children and adults, especially those requiring systemic medication [42].

Adverse effects of phototherapy are based on the depth of the UV ray penetration. Adverse effects of ultraviolet B include erythema, skin aging, and tanning, with no or only slightly increased risk of non-melanoma skin cancer. Adverse effects of psoralen ultraviolet light include erythema, burning, headache, itching, lentiginos, and nausea, with some risk of non-melanoma skin cancer, particularly squamous cell carcinoma. Adverse effects of 308 nm laser include burning, edema, erythema, hyperpigmentation, pruritus, and vesicles [13].

13.8 Systemic Therapies for Pruritus

Systemic therapies for pruritus should be saved for after topical pharmaceutical therapies have been attempted due to higher risk of adverse effects. There have been no randomized controlled trials finding one systemic medication to be safer or more effective than all the others [11]. The main systemic therapies for pruritus described here are listed in Table 13.4 and include: glucocorticoids, cyclosporine A, Ketotifen, antihistamines, opioid receptor modulators, lidocaine, SSRIs, TCAs, and neural

Table 13.4 Systemic pharmacological interventions for pruritus in atopic dermatitis

Antihistamines	Cetirizine 20 mg; cyproheptadine 4 mg; hydroxyzine 25 mg; diphenhydramine 25–50 mg	Anti-muscarinergic effects, sedation, anti-motion effects, arrhythmia, renal dysfunction
Cyclosporine A	2.5–4 mg/kg/day twice a day	Gingival hyperplasia, gout, headache, hyperlipidemia, hypertension, hypertrichosis, paresthesia, renal dysfunction; rarely infections and malignancies
Doxepin	Start at 10 mg at bedtime, increase every third day until the sedation is not tolerable	Anti-adrenergic, anti-serotonergic, anti-histaminic, arrhythmia
Glucocorticoids	Beclomethasone; flunisolide	Suppression of the hypothalamic- pituitary adrenal axis
Opioid receptor modulators	Start at naltrexone 25 mg daily, increase every 3–7 days	Cramping, diarrhea, headaches, nausea, vomiting
SSRIs, SNRIs neural modulators	Fluvoxamine 25–150 mg daily; mirtazapine 7.5–15 mg daily; paroxetine 10–40 mg daily; sertraline 75–50 mg daily	Appetite loss, insomnia, sexual dysfunction, weight loss, weight gain

modulators. It is important to consider the age of patient, arrhythmia risk, drug interactions, renal function, and sedation when selecting the proper systemic agent [11].

13.8.1 Antihistamines

Histamine is not known to be a chief mediator of pruritus in atopic dermatitis [31]. Large, randomized, controlled studies have not been conducted for the antipruritic effects of systemic antihistamines in atopic dermatitis; however, they are widely used as an adjunct therapy [32]. The soporific effect of antihistamines may reduce scratching during the night, thereby reducing the scratch-itch cycle of atopic dermatitis [33]. Thus, sedating antihistamines (cyproheptadine, hydroxyzine, diphenhydramine) may be more effective by improving sleep quality [32]. Normal doses of non-sedating antihistamines are not usually considered useful for the pruritus in atopic dermatitis unless urticaria or allergic rhinoconjunctivitis are present. Higher doses of non-sedating antihistamines have shown improvement in pruritus. One study has found 20 mg of cetirizine used daily for 4 weeks to be more effective than placebo in reducing pruritus [34]. If systemic anti-histamines are used, it is recommended to start with a higher dose of a non-sedating antihistamine in the daytime and a sedating antihistamine at night [11]. At higher doses, typically three to four times greater than recommended dosing for allergic rhinitis, non-sedating antihistamines are well tolerated and function as an anti-pruritic agent. For this reason, systemic antihistamines are considered first line of the systemic treatments for adjuvant treatment before other systemic medications. Systemic antihistamines are not

recommended without concurrent topical anti-inflammatory and anti-xerotic therapy. Antihistamines should be used with caution in the elderly due to potential for sedation and anti-cholinergic effects [11].

13.8.2 Glucocorticoids

Glucocorticoids have numerous anti-inflammatory effects including decreasing edema, inhibiting leukocyte migration, hindering phagocytosis, and blocking T lymphocyte cytokine release, which are all thought to suppress pruritus in patients with atopic dermatitis [11, 13]. Randomized controlled trials are limited on systemic glucocorticoid use for atopic dermatitis; however, one randomized controlled trial has found that 4 weeks of combined nasal and oral beclomethasone showed significantly decreased pruritus compared to placebo in patients with atopic dermatitis [34]. Another showed that 2 weeks of flunisolide nasal spray use in children with severe atopic dermatitis significantly reduced pruritus compared to placebo [35]. Glucocorticoids should be used with caution due to potential suppression of the hypothalamic-pituitary adrenal axis and rebound flares after tapering [11].

13.8.3 Cyclosporine A (CyA) & Immunosuppressants

Cyclosporine A binds intracellular cyclophilin receptor causing a decrease in T-lymphocyte activation and transcription of interleukin 2, which is thought to play a key role in pruritus [33]. It can be used off-label for the treatment of pruritus in patients with atopic dermatitis. Patients receiving cyclosporine A show a 55% reduction in pruritus after 6–8 weeks. The medication has been shown to be efficacious in both adults and children; however, pruritus returned after the medication was discontinued in 50% of patients [13]. Adverse effects of cyclosporine A are gingival hyperplasia, gout, headache, hyperlipidemia, hypertension, hypertrichosis, paresthesias, and renal dysfunction; infection and malignancies are rare [11].

Animal models have shown both tacrolimus and cyclosporine A may be better antipruritic agents than systemic glucocorticoids [11]. Additional studies have shown montelukast, mepolizumab, thymopentin, and rIFN- γ significantly reduce pruritus of atopic dermatitis by 12% compared to placebo [23]. The use of other systemic immunosuppressants including azathioprine, cyclophosphamide, and mycophenolate mofetil have not been well studied for pruritus in atopic dermatitis. Case series of the successful use of mycophenolate mofetil as an antipruritic drug for atopic dermatitis have been reported but without a control group [11]. Moreover, azathioprine may have potential use for photodermatitis-associated pruritus in adults and children with severe atopic dermatitis; however, hepatotoxicity and hepatitis have been observed with its use [11].

13.8.4 SSRIs, TCAs, and Neural Modulators

Selective serotonin reuptake inhibitors (SSRIs) block the reuptake of serotonin and thus increase the concentration of serotonin within the synaptic cleft. The mechanism of action in relation to pruritus is not understood, but SSRIs have been used to treat the pruritus associated with atopic dermatitis. Effectiveness has been documented with fluvoxamine, paroxetine, and sertraline for atopic dermatitis [11]. Adverse effects include appetite loss, insomnia, sexual dysfunction, and weight loss [11]. Serotonin-norepinephrine reuptake inhibitors (SNRIs) have not been thoroughly studied in atopic dermatitis [11].

TCAs block the serotonin transporter and the norepinephrine transporter, increasing the concentration of both serotonin and norepinephrine in the neural cleft. The difference among TCAs are their effects on adrenergic receptors, calcium channels, histamine receptors, N-Methyl-D-aspartate receptors, serotonin receptors, and sodium channels. Doxepin is a tricyclic antidepressant with anti-adrenergic and anti-serotonergic properties as well as potent H1 and H2 blocking properties. Low-dose doxepin is used in patients with atopic dermatitis [13]. However, the effectiveness of doxepin is not predictable. Adult patients should start at 10 mg of doxepin at bedtime, and then the dose should be gradually titrated upwards until itch control is achieved or the medication becomes too sedating. Because of their side effects, oral TCAs should be second or third-line therapy. No large controlled studies have compared the effects of TCAs, SSRIs or SNRIs [11].

Systemic neural modulators directly interact with nerves to reduce pruritus; however, their efficacy is not well established and there have been no randomized-controlled studies. This class of drugs includes amitriptyline, gabapentin, mirtazapine, paroxetine and pregabalin. These drugs are understudied; however, mirtazapine, paroxetine, and fluvoxamine have been reported to improve nocturnal pruritus in atopic dermatitis [36, 37]. The role of aprepitant, an anti-emetic which works as an antagonist of Substance P on neurokinin-1 receptors, has been studied in Sezary syndrome and prurigo nodularis but has not been studied in atopic dermatitis [13].

13.8.5 Opioid Receptor Modulators

Spinal μ and δ opioid receptors are activated by opioids providing analgesia, but they also cause or exacerbate pruritus [38]. The μ opioid receptor is found in the epidermis and dermis which can be blocked by opioid receptor modulators such as naltrexone and nalmefene. Studies with naltrexone and nalmefene for atopic dermatitis have shown variable results as anti-pruritic agents. Some studies have shown naltrexone and nalmefene to be superior to placebo in reducing pruritus, however others have shown no significant difference [13]. It is recommended to start the patient at a low dose of 10 mg of nalmefene daily or 25 mg of naltrexone daily, and increase the dose every 3–7 days to minimize adverse effects. Typical adverse

effects are cramping, diarrhea, headaches, nausea, and vomiting which are dose dependent and usually limited to the first 2 weeks of treatment [39]. Opioid receptor modulators should be considered second or third line agents due to mixed results and potential for tachyphylaxis. Kappa opioid receptor agonists such as butorphanol and nalfurafine (TRK-820) are thought to have the potential to be anti-pruritic agents but have not yet been formally investigated for atopic dermatitis [11, 13].

13.9 Immunosuppressants

Dupilumab is a fully human monoclonal antibody which binds to the IL-4 α receptor subunit, thereby inhibiting IL-4 and IL-13 signaling which are two primary cytokines necessary for Th2 response. In recent studies, the drug's deployment resulted in significant improvement in pruritus and visible disease state and is undergoing further testing in pediatric and adult patients for FDA approval. Using a Numerical Rating Scale, patients in one study on dupilumab monotherapy reported a statistically-significant 56% reduction in pruritus as compared to a 15% reduction seen in placebo at 12 weeks. Another study showed similar results with dupilumab monotherapy: a 53% reduction in pruritus on a Numerical Rating Scale versus 8% reduction for placebo at 12 weeks [40].

The use of other immunosuppressants as therapeutic agents including tested thymopentin, montelukast, mepolizumab, and rIFN- γ , significantly reduced the pruritus of AD by 12% in patients compared to placebo [23]. Tumor necrosis factor alpha antagonists, immunoglobulin E (omalizumab) receptor antagonists, interleukin 5 (mepolizumab) and CD20 (rituximab) antagonists have not demonstrated efficacy in atopic dermatitis [13]. Ketotifen is a mast cell stabilizer that has not shown to efficacy in treating pruritus in atopic dermatitis [11].

13.10 Summary of Recommendations for Anti-Pruritus Therapeutic Ladder

Pruritus has a significant impact on the quality of life in patients with atopic dermatitis. It is important that practitioners assess and record pruritus through questionnaires such as the Eppendorf Itch Questionnaire at each routine visit. Patients should employ non-pharmaceutical treatments such as emollients with wet wraps, elimination of triggers, changing scratching habits, and psychological interventions. If these methods of treatment are not successful or if the disease presentation is severe, patients should be treated based on the therapeutic ladder for treatment of pruritus shown in Fig. 13.3. First-line topical pharmaceutical agents should be prescribed, namely topical glucocorticoids and topical calcineurin inhibitors. Second-line topical agents can be used including coal tar, menthol, capsaicin, or doxepin. After the use of topical agents has been exhausted, primary systemic agents can be applied, such as sedating antihistamines, non-sedating antihistamines, oral glucocorticoids,

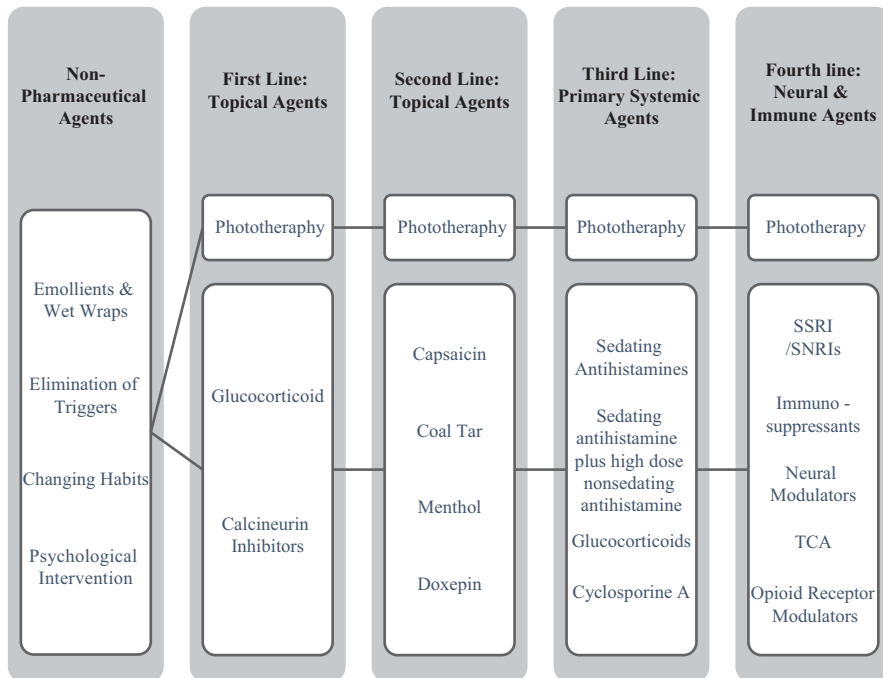


Fig. 13.3 Therapeutic ladder for treatment of pruritus in atopic dermatitis

or cyclosporine A. If primary systemic agents are found to be ineffective, neuro-modulating or immunomodulating agents can be used, including SSRI/SNRIs, TCAs, immunosuppressants, neural modulators, and opioid receptor modulators. Phototherapy has been shown to provide a dramatic improvement of pruritus in atopic dermatitis and can be used at any stage of treatment including as a first-line agent. Other agents include topical naltrexone, topical PEA, topical lidocaine, systemic Kappa opioid agonists, and immunosuppressants.

References

1. Romeo S. Atopic dermatitis: the itch that rashes. *Pediatr Nurs*. 1995;21(2):157–63.
2. Ring J, Senter T, Cornell R, Arroyave C, TAN E. Complement and immunoglobulin deposits in the skin of patients with atopic dermatitis. *Br J Dermatol*. 1978;99(5):495–501. doi:10.1111/j.1365-2133.1978.tb02016.x.
3. Shelley W. The neurohistology and neurophysiology of the itch sensation in man. *Arch Dermatol*. 1957;76(3):296. doi:10.1001/archderm.1957.01550210020004.
4. Ständer S, Gunzer M, Metzke D, Luger T, Steinhoff M. Localization of μ -opioid receptor 1A on sensory nerve fibers in human skin. *Regul Pept*. 2002;110(1):75–83. doi:10.1016/S0167-0115(02)00159-3.
5. Bastian B, van der Piepen U, Römisch J, Pâques E, Bröcker E. Localization of annexins in normal and diseased human skin. *J Dermatol Sci*. 1993;6(3):225–34. doi:10.1016/0923-1811(93)90043-o.

6. Johnson H, DeOreo G, Lascheid W, Mitchell F. Skin histamine levels in chronic atopic dermatitis**From the Division of Dermatology, Department of Medicine, Western Reserve University, School of Medicine, Cleveland, Ohio.(Aided by grant from Research and Development Division, Department of the Army, Contract #DA-49-007-MD-573). *J Invest Dermatol.* 1960;34(4):237–8. doi:[10.1038/jid.1960.38](https://doi.org/10.1038/jid.1960.38).
7. Connelly W, Shenton F, Lethbridge N, Leurs R, Waldvogel H, Faull R, et al. The histamine H4 receptor is functionally expressed on neurons in the mammalian CNS. *Br J Pharmacol.* 2009;157(1):55–63. doi:[10.1111/j.1476-5381.2009.00227.x](https://doi.org/10.1111/j.1476-5381.2009.00227.x).
8. Sonkoly E, Muller A, Lauerma A, Pivarcsi A, Soto H, Kemeny L, et al. IL-31: a new link between T cells and pruritus in atopic skin inflammation. *J Allergy Clin Immunol.* 2006;117(2):411–7. doi:[10.1016/j.jaci.2005.10.033](https://doi.org/10.1016/j.jaci.2005.10.033).
9. Wahlgren C, Hagermark O, Bergstrom R. The antipruritic effect of a sedative and a non-sedative antihistamine in atopic dermatitis. *Br J Dermatol.* 1990;122(4):545–51. doi:[10.1111/j.1365-2133.1990.tb14732.x](https://doi.org/10.1111/j.1365-2133.1990.tb14732.x).
10. Steinhoff M, Neisius U, Ikoma A, Fartasch M, Heyer G, Skov P, et al. Proteinase-activated receptor-2 mediates itch: a novel pathway for pruritus in human skin. *Exp Dermatol.* 2008;13(9):591. doi:[10.1111/j.0906-6705.2004.0212co.x](https://doi.org/10.1111/j.0906-6705.2004.0212co.x).
11. Steinhoff M, Cevikbas F, Ikoma A, Berger T. Pruritus: management algorithms and experimental therapies. *Seminars in Cutaneous Medicine and Surgery.* 2011;30(2):127–37. doi:[10.1016/j.sder.2011.05.001](https://doi.org/10.1016/j.sder.2011.05.001).
12. Darsow U, Scharein E, Simon D, Walter G, Bromm B, Ring J. New aspects of itch pathophysiology: component analysis of atopic itch using the 'Eppendorf Itch Questionnaire'. *Int Arch Allergy Immunol.* 2012;124(1–3):326–31. doi:[10.1159/000053748](https://doi.org/10.1159/000053748).
13. Hong J, Buddenkotte J, Berger T, Steinhoff M. Management of itch in atopic dermatitis. *Semin Cutan Med Surg.* 2011;30(2):71–86. doi:[10.1016/j.sder.2011.05.002](https://doi.org/10.1016/j.sder.2011.05.002).
14. Juenger M, Ladwig A, Staecker S, Arnold A, Kramer A, Daeschlein G, et al. Efficacy and safety of silver textile in the treatment of atopic dermatitis (AD). *Curr Med Res Opin.* 2006;22(4):739–50. doi:[10.1185/030079906x99990](https://doi.org/10.1185/030079906x99990).
15. Noren P, Melin L. The effect of combined topical steroids and habit-reversal treatment in patients with atopic dermatitis. *Br J Dermatol.* 1989;121(3):359–66. doi:[10.1111/j.1365-2133.1989.tb01430.x](https://doi.org/10.1111/j.1365-2133.1989.tb01430.x).
16. Arnold W. Tar. *Clin Dermatol.* 1997;15(5):739–44. doi:[10.1016/s0738-081x\(97\)00018-7](https://doi.org/10.1016/s0738-081x(97)00018-7).
17. Niordson A, Stahl D. Treatment of psoriasis with clintar cream. A controlled clinical trial. *Br J Clin Pract.* 1985;39:67–8.
18. Roelofzen J, Aben K, Oldenhof U, Coenraads P, Alkemade H, van de Kerkhof P, et al. No increased risk of cancer after coal tar treatment in patients with psoriasis or eczema. *J Invest Dermatol.* 2010;130(4):953–61. doi:[10.1038/jid.2009.389](https://doi.org/10.1038/jid.2009.389).
19. Yosipovitch G, Szolar C, Hui X, Maibach H. Effect of topically applied menthol on thermal, pain and itch sensations and biophysical properties of the skin. *Arch Dermatol Res.* 1996;288(5–6):245–8. doi:[10.1007/s004030050053](https://doi.org/10.1007/s004030050053).
20. Dray A. Neuropharmacological mechanisms of capsaicin and related substances. *Biochem Pharmacol.* 1992;44(4):611–5. doi:[10.1016/0006-2952\(92\)90393-w](https://doi.org/10.1016/0006-2952(92)90393-w).
21. Zhang W, Li Wan Po A. The effectiveness of topically applied capsaicin. *Eur J Clin Pharmacol.* 1994;46(6):517–22. doi:[10.1007/bf00196108](https://doi.org/10.1007/bf00196108).
22. Bonnel R, La Grenade L, Karwoski C, Beitz J. Allergic contact dermatitis from topical doxepin: food and drug administration's postmarketing surveillance experience. *J Am Acad Dermatol.* 2003;48(2):294–6. doi:[10.1067/mjd.2003.46](https://doi.org/10.1067/mjd.2003.46).
23. Sher L, Chang J, Patel I, Balkrishnan R, Fleischer A. PSS1 relieving the pruritus of atopic dermatitis: a meta-analysis. *Value Health.* 2012;15(4):A249–50. doi:[10.1016/j.jval.2012.03.1345](https://doi.org/10.1016/j.jval.2012.03.1345).
24. Berberian B, Breneman D, Drake L, Gratten D, Raimir S, Phillips S, et al. The addition of topical doxepin to corticosteroid therapy: an improved treatment regimen for atopic dermatitis. *Int J Dermatol.* 1999;38(2):145–7. doi:[10.1046/j.1365-4362.1999.00505.x](https://doi.org/10.1046/j.1365-4362.1999.00505.x).

25. Drake L, Fallon J, Sober A. Relief of pruritus in patients with atopic dermatitis after treatment with topical doxepin cream. *J Am Acad Dermatol.* 1994;31(4):613–6. doi:[10.1016/s0190-9622\(94\)70225-x](https://doi.org/10.1016/s0190-9622(94)70225-x).
26. Eberlein B, Eicke C, Reinhardt H, Ring J. Adjuvant treatment of atopic eczema: assessment of an emollient containing N-palmitoylethanolamine (ATOPA study). *J Eur Acad Dermatol Venereol.* 2007;22(1):73–82. doi:[10.1111/j.1468-3083.2007.02351.x](https://doi.org/10.1111/j.1468-3083.2007.02351.x).
27. Inan S, Dun N, Cowan A. Inhibitory effect of lidocaine on pain and itch using formalin-induced nociception and 5'-guanidinonaltrindole-induced scratching models in mice: behavioral and neuroanatomical evidence. *Eur J Pharmacol.* 2009;616(1–3):141–6. doi:[10.1016/j.ejphar.2009.06.026](https://doi.org/10.1016/j.ejphar.2009.06.026).
28. Krutmann J, Diepgen T, Luger T, Grabbe S, Meffert H, Sönnichsen N, et al. High-dose UVA1 therapy for atopic dermatitis: results of a multicenter trial. *J Am Acad Dermatol.* 1998;38(4):589–93. doi:[10.1016/s0190-9622\(98\)70123-9](https://doi.org/10.1016/s0190-9622(98)70123-9).
29. Der-Petrossian M, Seeber A, Hönigsmann H, Tanew A. Half-side comparison study on the efficacy of 8-methoxypsoralen bath-PUVA versus narrow-band ultraviolet B phototherapy in patients with severe chronic atopic dermatitis. *Br J Dermatol.* 2000;142(1):39–43. doi:[10.1046/j.1365-2133.2000.03239.x](https://doi.org/10.1046/j.1365-2133.2000.03239.x).
30. Nisticò S, Saraceno R, Capriotti E, Felice C, Chimenti S. Efficacy of monochromatic excimer light (308 nm) in the treatment of atopic dermatitis in adults and children. *Photomed Laser Surg.* 2008;26(1):14–8. doi:[10.1089/pho.2007.2116](https://doi.org/10.1089/pho.2007.2116).
31. Lewis T. The blood vessels of the human skin and their responses. *Arch Dermatol.* 1928;18(6):991. doi:[10.1001/archderm.1928.02380180188023](https://doi.org/10.1001/archderm.1928.02380180188023).
32. Klein P, Clark R. An evidence-based review of the efficacy of antihistamines in relieving pruritus in atopic dermatitis. *Arch Dermatol.* 1999;135(12):1522–5. doi:[10.1001/archderm.135.12.1522](https://doi.org/10.1001/archderm.135.12.1522).
33. Eichenfield L, Hanifin J, Luger T, Stevens S, Pride H. Consensus conference on pediatric atopic dermatitis. *J Am Acad Dermatol.* 2003;49(6):1088–95. doi:[10.1016/s0190-9622\(03\)02539-8](https://doi.org/10.1016/s0190-9622(03)02539-8).
34. Heddle R, Soothill J, Bulpitt C, Atherton D. Combined oral and nasal beclomethasone dipropionate in children with atopic eczema: a randomised controlled trial. *BMJ.* 1984;289(6446):651–4. doi:[10.1136/bmj.289.6446.651](https://doi.org/10.1136/bmj.289.6446.651).
35. La Rosa M, Musarra I, Ranno C, Maiello N, Negri L, del Giudice M, et al. A randomized, double-blind, placebo-controlled, crossover trial of systemic flunisolide in the treatment of children with severe atopic dermatitis. *Curr Ther Res.* 1995;56(7):720–6. doi:[10.1016/0011-393x\(95\)85143-7](https://doi.org/10.1016/0011-393x(95)85143-7).
36. Hundley J, Yosipovitch G. Mirtazapine for reducing nocturnal itch in patients with chronic pruritus: a pilot study. *J Am Acad Dermatol.* 2004;50(6):889–91. doi:[10.1016/j.jaad.2004.01.045](https://doi.org/10.1016/j.jaad.2004.01.045).
37. Ständer S, Böckenholt B, Schürmeyer-Horst F, Weishaupt C, Heuft G, Schneider T. Treatment of chronic pruritus with the selective serotonin re-uptake inhibitors paroxetine and fluvoxamine: results of an open-labelled, two-arm proof-of-concept study. *Acta Derm Venereol.* 2009;89(1):45–51. doi:[10.2340/00015555-0553](https://doi.org/10.2340/00015555-0553).
38. Ständer S, Schmelz M. Chronic itch and pain-similarities and differences. *Eur J Pain.* 2006;10(5):473–8. doi:[10.1016/j.ejpain.2006.03.005](https://doi.org/10.1016/j.ejpain.2006.03.005).
39. Phan N, Bernhard J, Luger T, Ständer S. Antipruritic treatment with systemic μ -opioid receptor antagonists: a review. *J Am Acad Dermatol.* 2010;63(4):680–8. doi:[10.1016/j.jaad.2009.08.052](https://doi.org/10.1016/j.jaad.2009.08.052).
40. Blakely K, Gooderham M, Papp K. Dupilumab, a monoclonal antibody for atopic dermatitis: a review of current literature. *Skin Therapy.* 2016;21(2):1–5.
41. Brenninkmeijer E, Spuls P, Lindeboom R, Van Der Wal A, Bos J, Wolkerstorfer A. Excimer laser vs. clobetasol propionate 0.05% ointment in prurigo form of atopic dermatitis: a randomized controlled trial, a pilot. *Br J Dermatol.* 2010;163(4):823–31. doi:[10.1111/j.1365-2133.2010.09858.x](https://doi.org/10.1111/j.1365-2133.2010.09858.x).
42. Goeckerman W. The treatment of psoriasis. *Northwest Med.* 1925;24:229–31, 211.