

Management of Itch in Atopic Dermatitis

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

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 alopecia 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. *Semin Cutan Med Surg* 30:71-86 © 2011 Elsevier Inc. All rights reserved.

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 unmyelinated 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 I 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 I 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

*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.

Dr. Judith Hong, Dr. Joerg Buddenkotte and Dr. Timothy G. Berger have nothing to disclose. Dr. Steinhoff has performed consultancy services for which he received compensation for Galderma, Merck, Sanofi-Aventis and Regeneron. On behalf of Dr. Steinhoff, his institution has received financial gifts from Maruho (Japan), and research was supported by ZymoGenetics, L’Oreal and Galderma.

Address reprint requests to Martin Steinhoff, MD, PhD, Departments of Dermatology and Surgery, University of California San Francisco, 513 Parnassus Avenue, Room S-1268, San Francisco, CA, 94143. E-mail: steinhoffm@derm.ucsf.edu

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 | <ul style="list-style-type: none"> ● Avoiding exogenous triggers (see Table 2) ● Antimicrobials for overt secondary infection ● Stress management | <ul style="list-style-type: none"> ● Food allergen avoidance in symptomatic patients | <ul style="list-style-type: none"> ● Bacterial decolonization ● Food allergen avoidance in asymptomatic patients ● Dust-mite reduction |
| Topical therapy | <ul style="list-style-type: none"> ● Emollients ● Corticosteroids | <ul style="list-style-type: none"> ● Calcineurin inhibitors* ● Coal tar | <ul style="list-style-type: none"> ● Menthol ● Capsaicin ● Naltrexone ● Doxepin |
| Systemic therapy | | <ul style="list-style-type: none"> ● Oral sedating antihistamines (minimal evidence in AD, but soporific effect may be helpful) ● Combination of nonsedating and sedating antihistamines (high-dose) ● Cyclosporine A ● Corticosteroids | <ul style="list-style-type: none"> ● Other immunosuppressants (eg, azathioprine, mycophenolate mofetil, methotrexate, interferon-gamma) ● Mu-opiate receptor antagonists ● Kappa-opioid agonist ● Neurogenic agents (eg, gabapentin, mirtazapine, paroxetine) |
| Other | <ul style="list-style-type: none"> ● Education about disease and treatment modalities ● Written instructions and/or handouts in addition to verbal instructions | <ul style="list-style-type: none"> ● Phototherapy (UVA, UVA1, UVB, Combination, PUVA) ● Goeckerman (phototherapy + tar) ● Psychological interventions (eg, cognitive-behavioral therapy, habit reversal therapy, autogenic training) | <ul style="list-style-type: none"> ● Excimer laser ● Herbals and botanicals ● Hypnotherapy ● Massage ● Biofeedback ● Acupuncture |

AD, atopic dermatitis.

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

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 in-

creased 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 adults⁵³ 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

Table 2 Trigger Factors in AD for Consideration in the Long-Term Management of AD

| | |
|-------------------------|---|
| Allergies | House dust mites, food allergens, air-borne contact dermatitis (pollen, etc), animals, jewelry. |
| Infections | <i>Staphylococcus aureus</i> , viral infections (herpes, molluscum), yeasts (eg, <i>Trichophyton</i> , 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.

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) anti-inflammatory 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 AD⁶⁷ 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 defects⁷⁰ are some, but probably not all, barrier defects in AD skin. Moisturizers play an important part in the management of AD⁷¹ 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 ointment⁹⁸ and 0.1% acemetasone dipropionate⁹⁹ and was similar in efficacy to 0.1% hydrocortisone-butyrate ointment.¹⁰⁰ The most common side effects reported from TCI¹ 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 Unguentum 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 prop-

erties. 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 innocuous 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 patients¹¹⁹; 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 inflammation¹²⁵ 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 endocannabinoids such as N-arachidonoyl-ethanolamine (AEA). PEA has been found to have anti-inflammatory and analgesic effects; postulated mechanisms include downregulation of mast-cell degranulation¹⁴¹ 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 neuro-modulators, 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 al¹⁵¹ 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- α blockers have been described as either minimally effective¹⁶⁴ 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 photochemotherapy¹⁶⁹ 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 epidermis¹⁷⁹ 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 butorphanol¹⁸⁸ 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 syndrome¹⁹³ 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 flucortolone 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, pruritus 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 propi-

onate, 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 AD²³⁴ 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 patients²⁶⁶ 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

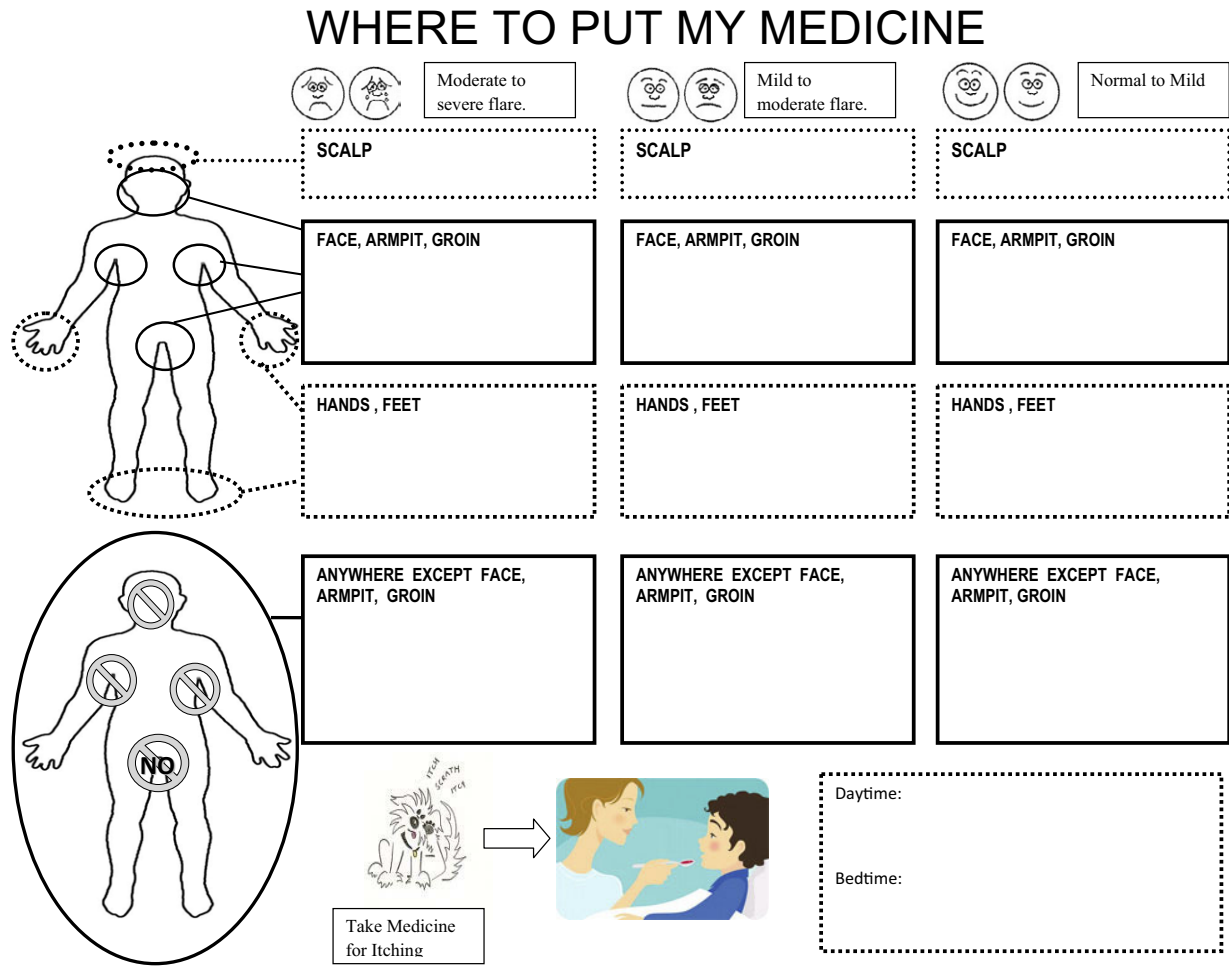


Figure 1 Visual aid for patient medication in children.

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 dietitians.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 cen-

ters 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.

References

- Rothman S: Physiology of itching. *Physiol Rev* 21:357-381, 1941
- Hanifin JM, Rajka G: Diagnostic features of atopic dermatitis. *Acta Derm Venereol (Stockh) Suppl* 92:44-47, 1980
- Romeo SP: Atopic dermatitis: The itch that rashes. *Pediatr Nurs* 21: 157-163, 1995
- Buske-Kirschbaum A, Geiben A, Hellhammer D: Psychobiological aspects of atopic dermatitis: An overview. *Psychother Psychosom* 70:6-16, 2001
- Finlay AY, Khan GK: Dermatology Life Quality Index (DLQI)—A simple practical measure for routine clinical use. *Clin Exp Dermatol* 19:210-216, 1994
- Cevikbas F, Steinhoff M, Ikoma A: Role of spinal neurotransmitter receptors in itch: New insights into therapies and drug development. *CNS Neurosci Ther* 17: 2011, doi: 10.1111/j.1755-5949.2010.00201.x
- Paus R, Schmelz M, Biró T, et al: Frontiers in pruritus research: Scratching the brain for more effective itch therapy. *J Clin Invest* 116:1174-1186, 2006
- Sun YG, Chen ZF: A gastrin-releasing peptide receptor mediates the itch sensation in the spinal cord. *Nature* 448:700-703, 2007
- Sun YG, Zhao ZQ, Meng XL, et al: Cellular basis of itch sensation. *Science* 325:1531-1534, 2009
- Williams DH: Skin temperature reaction to histamine in atopic dermatitis (Disseminated neurodermatitis). *J Invest Dermatol* 1:119-129, 1938
- Steinhoff M, Neisius U, Ikoma A, et al: Proteinase-activated receptor-2 mediates itch: A novel pathway for pruritus in human skin. *J Neurosci* 23:6176-6180, 2003
- Steinhoff M, Vergnolle N, Young SH, et al: Agonists of proteinase-activated receptor 2 induce inflammation by a neurogenic mechanism. *Nat Med* 6:151-158, 2000
- Akiyama T, Merrill AW, Carstens MI, et al: Activation of superficial dorsal horn neurons in the mouse by a PAR-2 agonist and 5-HT: Potential role in itch. *J Neurosci* 29:6691-6699, 2009
- Anand P, Springall DR, Blank MA, et al: Neuropeptides in skin disease: Increased VIP in eczema and psoriasis but not axillary hyperhidrosis. *Br J Dermatol* 124:547-549, 1991
- Fantini F, Pincelli C, Romualdi P, et al: Levels are decreased in lesional skin of atopic dermatitis. *Exp Dermatol* 1:127-128, 1992
- Heyer G, Vogelgsang M, Hornstein OP: Acetylcholine is an inducer of itching in patients with atopic eczema. *J Dermatol* 24:621-625, 1997
- Gaspari AA, Lotze MT, Rosenberg SA, et al: Dermatologic changes associated with interleukin 2 administration. *JAMA* 258:1624-1629, 1987
- Grewe M, Vogelgsang K, Ruzicka T, et al: Neurotrophin-4 production by human epidermal keratinocytes: Increased expression in atopic dermatitis. *J Invest Dermatol* 114:1108-1112, 2000
- Fjellner B, Hägermark O: Experimental pruritus evoked by platelet activating factor (PAF-acether) in human skin. *Acta Derm Venereol* 65:409-412, 1985
- Andoh T, Kuraishi Y: Intradermal leukotriene B₄, but not prostaglandin E₂, induces itch-associated responses in mice. *Eur J Pharmacol* 353:93-96, 1998
- Ikoma A, Steinhoff M, Ständer S, et al: The neurobiology of itch. *Nat Rev Neurosci* 7:535-547, 2006
- Pincelli C, Fantini F, Massimi P, et al: Neuropeptides in skin from patients with atopic dermatitis: An immunohistochemical study. *Br J Dermatol* 122:745-750, 1990
- Basbaum AI, Bautista DM, Scherrer G, et al: Cellular and molecular mechanisms of pain. *Cell* 139:267-284, 2009
- Ma Q: Labeled lines meet and talk: Population coding of somatic sensations. *J Clin Invest* 120:3773-3778, 2010
- Hosogi M, Schmelz M, Miyachi Y, et al: Bradykinin is a potent pruritogen in atopic dermatitis: A switch from pain to itch. *Pain* 126:16-23, 2006
- Cevikbas F, Steinhoff A, Homey B, et al: Neuroimmune interactions in allergic skin diseases. *Curr Opin Allergy Clin Immunol* 7:365-373, 2007
- Sonkoly E, Muller A, Lauerma AI, et al: IL-31: A new link between T cells and pruritus in atopic skin inflammation. *J Allergy Clin Immunol* 117:411-417, 2006
- Darsow U, Pfab F, Valet M, et al: Pruritus and Atopic Dermatitis. *Clin Rev Allergy Immunol*, 2011. [Epub ahead of print]
- Metz M, Ständer S: Chronic pruritus—Pathogenesis, clinical aspects and treatment. *J Eur Acad Dermatol Venereol* 24:1249-1260, 2010
- Buddenkotte J, Steinhoff M: Pathophysiology and therapy of pruritus in allergic and atopic diseases. *Allergy* 65:805-821, 2010
- Hanifin JM: Basic and clinical aspects of atopic dermatitis. *Ann Allergy* 52:386-395, 1984
- Rovensky J, Saxl O: Differences in the dynamics of sweat secretion in atopic children. *J Invest Dermatol* 43:171-176, 1964
- Kurzen H, Schallreuter KU: Novel aspects in cutaneous biology of acetylcholine synthesis and acetylcholine receptors. *Exp Dermatol* 13 Suppl 4(suppl 4):27-30, 2004
- Rajka G: Essential Aspects of Atopic Dermatitis. Berlin, Springer-Verlag, 1989, pp 57-69, 212, 1761
- Bendsøe N, Björnberg A, Asnes H: Itching from wool fibres in atopic dermatitis. *Contact Dermatitis* 17:21-22, 1987
- Wahlgren CF, Hägermark O, Bergström R: Patients' perception of itch induced by histamine, compound 48/80 and wool fibres in atopic dermatitis. *Acta Derm Venereol* 71:488-494, 1991
- Gauger A, Fischer S, Mempel M, et al: Efficacy and functionality of silver-coated textiles in patients with atopic eczema [Erratum in: *J Eur Acad Dermatol Venereol* 2006 20(6):771]. *J Eur Acad Dermatol Venereol* 20:534-541, 2006
- Gauger A: Silver-coated textiles in the therapy of atopic eczema. *Curr Probl Dermatol* 33:152-164, 2006
- Hassing JH, Nater JP, Bleumink E: Irritancy of low concentrations of soap and synthetic detergents as measured by skin water loss. *Dermatologica* 164:314-321, 1982
- Effendy I, Maibach HI: Detergent and skin irritation. *Clin Dermatol* 14:15-21, 1996
- Morren MA, Przybilla B, Bamelis M, et al: Atopic dermatitis: Triggering factors. *J Am Acad Dermatol* 31:467-473, 1994
- Vocks E, Busch R, Fröhlich C, et al: Influence of weather and climate on subjective symptom intensity in atopic eczema. *Int J Biometeorol* 45:27-33, 2001
- Darsow U, Vieluf D, Ring J: Evaluating the relevance of aeroallergen sensitization in atopic eczema with the atopy patch test: A randomized, double-blind multicenter study. *Atopy Patch Test Study Group. J Am Acad Dermatol* 40:187-193, 1999
- Holm L, Bengtsson A, van Hage-Hamsten M, et al: Effectiveness of occlusive bedding in the treatment of atopic dermatitis—A placebo-controlled trial of 12 months' duration. *Allergy* 56:152-158, 2001
- Tan BB, Weald D, Strickland I, et al: Double-blind controlled trial of effect of housedust-mite allergen avoidance on atopic dermatitis. *Lancet* 347:15-18, 1996
- Sanda T, Yasue T, Ohashi M, et al: Effectiveness of house dust-mite allergen avoidance through clean room therapy in patients with atopic dermatitis. *J Allergy Clin Immunol* 89:653-657, 1992
- Friedmann PS: Dust mite avoidance in atopic dermatitis. *Clin Exp Dermatol* 24:433-437, 1999
- Sampson HA: Role of immediate food hypersensitivity in the pathogenesis of atopic dermatitis. *J Allergy Clin Immunol* 71:473-480, 1983

49. Niggemann B, Sielaff B, Beyer K, et al: Outcome of double-blind, placebo-controlled food challenge tests in 107 children with atopic dermatitis. *Clin Exp Allergy* 29:91-96, 1999
50. Niggemann B, Reibel S, Roehr CC, et al: Predictors of positive food challenge outcome in non-IgE-mediated reactions to food in children with atopic dermatitis. *J Allergy Clin Immunol* 108:1053-1058, 2001
51. Breuer K, Heratizadeh A, Wulf A, et al: Late eczematous reactions to food in children with atopic dermatitis. *Clin Exp Allergy* 34:817-824, 2004
52. Bath-Hextall F, Delamere FM, Williams HC: Dietary exclusions for improving established atopic eczema in adults and children: Systematic review. *Allergy* 64:258-264, 2009
53. Sicherer SH, Sampson HA: Food hypersensitivity and atopic dermatitis: Pathophysiology, epidemiology, diagnosis, and management. *J Allergy Clin Immunol* 104:S114-S122, 1999
54. Bock SA: The natural history of food sensitivity. *J Allergy Clin Immunol* 69:173-117, 1982
55. Suh KY: Food allergy and atopic dermatitis: Separating fact from fiction. *Semin Cutan Med Surg* 29:72-78, 2010
56. Leung DY, Harbeck R, Bina P, et al: Presence of IgE antibodies to staphylococcal exotoxins on the skin of patients with atopic dermatitis. Evidence for a new group of allergens. *J Clin Invest* 92:1374-1380, 1993
57. Leyden JJ, Marples RR, Kligman AM: *Staphylococcus aureus* in the lesions of atopic dermatitis. *Br J Dermatol* 525-30, 1974
58. Arslanagic N, Arslanagic R: Atopic dermatitis and *Staphylococcus aureus*. *Med Arh* 58:363-365, 2004
59. William REA, Gibson AG, Aitchison TC, et al: Assessment of a contact-plate sampling technique and subsequent quantitative bacterial studies in atopic dermatitis. *Br J Dermatol* 123:493-501, 1990
60. Abeck D, Mempel M: *Staphylococcus aureus* colonization in atopic dermatitis and its therapeutic implications. *Br J Dermatol* 139 Suppl 53 suppl 53:13-16, 1998
61. Boguniewicz M, Sampson H, Leung SB, et al: Effects of cefuroxime axetil on *Staphylococcus aureus* colonization and superantigen production in atopic dermatitis. *J Allergy Clin Immunol* 108:651-652, 2001
62. Breuer K, Haussler S, Kapp A, et al: *Staphylococcus aureus*: Colonizing features and influence of an antibacterial treatment in adults with atopic dermatitis. *Br J Dermatol* 147:55-61, 2002
63. Birnie AJ, Bath-Hextall FJ, Ravenscroft JC, et al: Interventions to reduce *Staphylococcus aureus* in the management of atopic eczema. *Cochrane Database Syst Rev* 3:CD003871, 2008
64. Darso U, Wollenberg A, Simon D, et al: ETFAD/EADV eczema task force 2009 position paper on diagnosis and treatment of atopic dermatitis. *J Eur Acad Dermatol Venereol* 24:317-328, 2010
65. Lübke J: Secondary infections in patients with atopic dermatitis. *Am J Clin Dermatol* 4:641-654, 2003
66. Hirsch T, Koerber A, Jacobsen F, et al: Evaluation of toxic side effects of clinically used skin antiseptics in vitro. *J Surg Res* 164:344-350, 2010
67. Elias PM, Hatano Y, Williams ML: Basis for the barrier abnormality in atopic dermatitis: Outside-inside-outside pathogenic mechanisms. *J Allergy Clin Immunol* 121:1337-1343, 2008
68. Werner Y, Lindberg M: Transepidermal water loss in dry and clinically normal skin in patients with atopic dermatitis. *Acta Derm Venereol* 65:102-105, 1985
69. Yamamoto A, Serizawa S, Ito M, et al: Stratum corneum lipid abnormalities in atopic dermatitis. *Arch Dermatol Res* 283:219-223, 1991
70. Weidinger S, O'Sullivan M, Illig T, et al: Filaggrin mutations, atopic eczema, hay fever, and asthma in children. *J Allergy Clin Immunol* 121:1203-1209, 2008
71. Cheong WK: Gentle cleansing and moisturizing for patients with atopic dermatitis and sensitive skin. *Am J Clin Dermatol* 10 Suppl 1:13-17, 2009
72. Vilaplana J, Coll J, Trullás C, et al: Clinical and non-invasive evaluation of 12% ammonium lactate emulsion for the treatment of dry skin in atopic and non-atopic subjects. *Acta Derm Venereol* 72:28-33, 1992
73. Msika P, De Belilovsky C, Piccardi N, et al: New emollient with topical corticosteroid-sparing effect in treatment of childhood atopic dermatitis: SCORAD and quality of life improvement. *Pediatr Dermatol* 25:606-612, 2008
74. Grimalt R, Mengeaud V, Cambazard F, Study Investigators Group: The steroid-sparing effect of an emollient therapy in infants with atopic dermatitis: A randomized controlled study. *Dermatology* 214:61-67, 2007
75. Lucky AW, Leach AD, Laskarzewski P, et al: Use of an emollient as a steroid-sparing agent in the treatment of mild to moderate atopic dermatitis in children. *Pediatr Dermatol* 14:321-324, 1997
76. Hanifin JM, Hebert AA, Mays SR, et al: Effects of a low-potency corticosteroid lotion plus a moisturizing regimen in the treatment of atopic dermatitis. *Curr Ther Resources* 59:227-233, 1998
77. Szczepanowska J, Reich A, Szepietowski JC: Emollients improve treatment results with topical corticosteroids in childhood atopic dermatitis: A randomized comparative study. *Pediatr Allergy Immunol* 19:614-618, 2008
78. Chamlin SL, Kao J, Frieden IJ, et al: Ceramide-dominant barrier repair lipids alleviate childhood atopic dermatitis: Changes in barrier function provide a sensitive indicator of disease activity. *J Am Acad Dermatol* 47:198-208, 2002
79. Sugarman JL, Parish LC: Efficacy of a lipid-based barrier repair formulation in moderate-to-severe pediatric atopic dermatitis. *J Drugs Dermatol* 8:1106-1111, 2009
80. Hachisuka J, Takeuchi S, Kido M, et al: Severity of disease, rather than xerosis, correlates with pruritus in patients with atopic dermatitis. *Int J Dermatol* 48:374-378, 2009
81. Wollenberg A, Frank R, Kroth J, et al: Proactive therapy of atopic eczema—An evidence-based concept with a behavioral background. *J Dtsch Dermatol Ges* 7:117-121, 2009
82. Thiers BH: Topical steroid therapy of atopic skin diseases. *Allergy Proc* 10:413-416, 1989
83. Maloney JM, Morman MR, Stewart DM, et al: Clobetasol propionate emollient 0.05% in the treatment of atopic dermatitis. *Int J Dermatol* 37:142-144, 1998
84. Jorizzo J, Levy M, Lucky A, et al: Multicenter trial for long-term safety and efficacy comparison of 0.05% desonide and 1% hydrocortisone ointments in the treatment of atopic dermatitis in pediatric patients. *J Am Acad Dermatol* 33:74-77, 1995
85. Eichenfield LF, Miller BH, Cutivate Lotion Study Group: Two randomized, double-blind, placebo-controlled studies of fluticasone propionate lotion 0.05% for the treatment of atopic dermatitis in subjects from 3 months of age. *J Am Acad Dermatol* 54:715-717, 2006
86. Wolkerstorfer A, Strobos MA, Glazenburg EJ, et al: Fluticasone propionate 0.05% cream once daily versus clobetasone butyrate 0.05% cream twice daily in children with atopic dermatitis. *J Am Acad Dermatol* 39:226-231, 1998
87. Del Rosso JQ, Bhambri S: Daily application of fluocinonide 0.1% cream for the treatment of atopic dermatitis. *J Clin Aesthet Dermatol* 2:24-32, 2009
88. Nicol NH: Atopic dermatitis: The (wet) wrap-up. *Am J Nurs* 87:1560-1563, 1987
89. Goodyear HM, Harper JL: "Wet-wrap" dressings for eczema: An effective treatment but not to be misused. *Br J Dermatol* 146:159, 2002
90. Wolkerstorfer A, Visser RL, De Waard van der Spek FB, et al: Efficacy and safety of wet-wrap dressings in children with severe atopic dermatitis: Influence of corticosteroid dilution. *Br J Dermatol* 143:999-1004, 2000
91. Schnopp C, Holtmann C, Stock S, et al: Topical steroids under wet-wrap dressings in atopic dermatitis—a vehicle-controlled trial. *Dermatology (Basel)* 204:56-59, 2002
92. Devillers AC, Oranje AP: Efficacy and safety of "wet-wrap" dressings as an intervention treatment in children with severe and/or refractory atopic dermatitis: A critical review of the literature. *Br J Dermatol* 154:579-585, 2006
93. Boguniewicz M, Fiedler VC, Raimer S, et al: A randomized, vehicle-controlled trial of tacrolimus ointment for treatment of atopic derma-

- titis in children. Pediatric Tacrolimus Study Group. *J Allergy Clin Immunol* 102:637-644, 1998
94. Hanifin JM, Ling MR, Langley R, et al: Tacrolimus ointment for the treatment of atopic dermatitis in adult patients: part I, Efficacy. *J Am Acad Dermatol* 44 Suppl 1:S28-S38, 2001
 95. Hon KL, Lam MC, Leung TF, et al: Assessing itch in children with atopic dermatitis treated with tacrolimus: Objective versus subjective assessment. *Adv Ther* 24:23-28, 2007
 96. Paller AS, Lebowitz M, Fleischer AB Jr, et al: Tacrolimus ointment is more effective than pimecrolimus cream with a similar safety profile in the treatment of atopic dermatitis: Results from 3 randomized, comparative studies. *J Am Acad Dermatol* 52:810-822, 2005
 97. Kempers S, Boguniewicz M, Carter E, et al: A randomized investigator-blinded study comparing pimecrolimus cream 1% with tacrolimus ointment 0.03% in the treatment of pediatric patients with moderate atopic dermatitis. *J Am Acad Dermatol* 51:515-525, 2004
 98. Reitamo S, Van Leent EJ, Ho V, et al: European/Canadian Tacrolimus Ointment Study Group. Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone acetate ointment in children with atopic dermatitis. *J Allergy Clin Immunol* 109:539-546, 2002
 99. Nakagawa H: Comparison of the efficacy and safety of 0.1% tacrolimus ointment with topical corticosteroids in adult patients with atopic dermatitis: Review of randomised, double-blind clinical studies conducted in Japan. *Clin Drug Invest* 26:235-246, 2006
 100. Reitamo S, Rustin M, Ruzicka T, et al: Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone butyrate ointment in adult patients with atopic dermatitis. *J Allergy Clin Immunol* 109:547-555, 2002
 101. Fleischer AB Jr, Boguniewicz M: An approach to pruritus in atopic dermatitis: A critical systematic review of the tacrolimus ointment literature. *J Drugs Dermatol* 9:488-498, 2010
 102. Slutsky JB, Clark RA, Remedios AA, et al: An evidence-based review of the efficacy of coal tar preparations in the treatment of psoriasis and atopic dermatitis. *J Drugs Dermatol* 9:1258-1264, 2010
 103. Arnold WP: Tar. *Clin Dermatol* 15:739-744, 1997
 104. Thami GP, Sarkar R: Coal tar: Past, present and future. *Clin Exp Dermatol* 27:99-103, 2002
 105. Niordson AM, Stahl D: Treatment of psoriasis with Clinitar cream. A controlled clinical trial. *Br J Clin Pract* 39:67-68, 72, 1985
 106. Munkvad M: A comparative trial of Clinitar versus hydrocortisone cream in the treatment of atopic eczema. *Br J Dermatol* 121:763-766, 1989
 107. van der Valk PG, Snater E, Verbeek-Gijsbers W, et al: Out-patient treatment of atopic dermatitis with crude coal tar. *Dermatology (Basel)* 193:41-44, 1996
 108. Brockow K, Grabenhorst P, Abeck D, et al: Effect of gentian violet, corticosteroid and tar preparations in *Staphylococcus-aureus*-colonized atopic eczema. *Dermatology (Basel)* 199:231-236, 1999
 109. Burden AD, Muston H, Beck MH: Intolerance and contact allergy to tar and dithranol in psoriasis. *Contact Dermatitis* 31:185-186, 1994
 110. Lin AN, Moses K: Tar-revisited. *Int J Dermatol* 24:216-218, 1985
 111. Boffetta P, Jourenkova N, Gustavsson P: Cancer risk from occupational and environmental exposure to polycyclic aromatic hydrocarbons. *Cancer Causes Control* 8:444-472, 1997
 112. Roelofzen JH, Aben KK, Oldenhof UT, et al: No increased risk of cancer after coal tar treatment in patients with psoriasis or eczema. *J Invest Dermatol* 130:953-961, 2010
 113. Maughan WZ, Muller SA, Perry HO, et al: Incidence of skin cancers in patients with atopic dermatitis treated with coal tar. A 25-year follow-up study. *J Am Acad Dermatol* 3:612-615, 1980
 114. Paghdal KV, Schwartz RA: Topical tar: Back to the future. *J Am Acad Dermatol* 61:294-302, 2009
 115. Patel T, Ishiui Y, Menthol YG: A refreshing look at this ancient compound. *J Am Acad Dermatol* 57:873-878, 2007
 116. Peier AM, Moqrich A, Hergarden AC, et al: A TRP channel that senses cold stimuli and menthol. *Cell* 108:705-715, 2002
 117. Bromm B, Scharein E, Darsow U, et al: Effects of menthol and cold on histamine-induced itch and skin reactions in man. *Neurosci Lett* 187:157-160, 1995
 118. Galeotti N, Di Cesare ML, Mazzanti G, et al: A natural analgesic compound. *Neurosci Lett* 322:145-148, 2002
 119. Fruhstorfer H, Hermanns M, Latzke L: The effects of thermal stimulation on clinical and experimental itch. *Pain* 24:259-269, 1986
 120. Steinhoff M, Bienenstock J, Schmelz M, et al: Neurophysiological, neuroimmunological, and neuroendocrine basis of pruritus. *J Invest Dermatol* 126:1705-1718, 2006
 121. Riser RL, Kowcz A, Schoelermann A, et al: Tolerance profile and efficacy of a menthol-containing itch relief spray in children and atopics. *Pediatr Dermatol* 194 Suppl 64:S83, 2003
 122. Wilkinson SM, Beck MH: Allergic contact dermatitis from menthol in peppermint. *Contact Dermatitis* 30:42-43, 1994
 123. Hatem S, Attal N, Willer JC, et al: Psychophysical study of the effects of topical application of menthol in healthy volunteers. *Pain* 122:190-196, 2006
 124. Yosipovitch G, Szolar C, Hui XY, et al: Effect of topically applied menthol on thermal, pain and itch sensations and biophysical properties of the skin. *Arch Dermatol Res* 288:245-248, 1996
 125. Jancsó N, Jancsó-Gábor A, Szolcsányi J: Direct evidence for neurogenic inflammation and its prevention by denervation and by pretreatment with capsaicin. *Br J Pharmacol Chemother* 31:138-151, 1967
 126. Tarng DC, Cho YL, Liu HN, Huang TP: Hemodialysis-related pruritus: A double-blind, placebo-controlled, crossover study of capsaicin 0.025% cream. *Nephron* 72:617-622, 1996
 127. Wallengren J, Klinker M: Successful treatment of notalgia paresthetica with topical capsaicin: Vehicle-controlled, double-blind, crossover study. *J Am Acad Dermatol* 32:287-289, 1995
 128. Ständer S, Luger T, Metzke D: Treatment of prurigo nodularis with topical capsaicin. *J Am Acad Dermatol* 44:471-478, 2001
 129. Caterina MJ, Schumacher MA, Tominaga M, et al: The capsaicin receptor: A heat-activated ion channel in the pain pathway. *Nature* 389:816-824, 1997
 130. Dray A: Neuropharmacological mechanisms of capsaicin and related substances. *Biochem Pharmacol* 44:611-615, 1992
 131. Zhang WY, Li W, Po A: The effectiveness of topically applied capsaicin: A meta-analysis. *Eur J Clin Pharmacol* 46:517-522, 1994
 132. Gooding SM, Canter PH, Coelho HF, et al: Systematic review of topical capsaicin in the treatment of pruritus. *Int J Dermatol* 49:858-865, 2010
 133. Drake LA, Fallon JD, Sober A: Relief of pruritus in patients with atopic dermatitis after treatment with topical doxepin cream. The doxepin study group. *J Am Acad Dermatol* 31:613-616, 1994
 134. Berberian BJ, Breneman DL, Drake LA, et al: The addition of topical doxepin to corticosteroid therapy: An improved treatment regimen for atopic dermatitis. *Int J Dermatol* 38:145-148, 1999
 135. Hoare C, Li W, Po A, et al: Systematic review of treatments for atopic eczema. *Health Technol Assess* 4:1-191, 2000
 136. Bonnel RA, La Grenade L, Karwoski CB, et al: Allergic contact dermatitis from topical doxepin: Food and Drug Administration's postmarketing surveillance experience. *J Am Acad Dermatol* 48:294-296, 2003
 137. Eschler DC, Klein PA: An evidence-based review of the efficacy of topical antihistamines in the relief of pruritus. *J Drugs Dermatol* 9:992-997, 2010
 138. Bigliardi PL, Stammer H, Jost G, et al: Treatment of pruritus with topically applied opiate receptor antagonist. *J Am Acad Dermatol* 56:979-988, 2007
 139. Rukwied R, Watkinson A, McGlone F, et al: Cannabinoid agonists attenuate capsaicin-induced responses in human skin. *Pain* 102:283-288, 2003
 140. Dvorak M, Watkinson A, McGlone F, et al: Histamine induced responses are attenuated by a cannabinoid receptor agonist in human skin. *Inflamm Res* 52:238-245, 2003
 141. Aloe L, Leon A, Levi-Montalcini R: A proposed autacoid mechanism controlling mastocyte behaviour. *Agents Actions* 1993;39 Spec No: C145-7.
 142. Conti S, Costa B, Colleoni M, et al: Antiinflammatory action of endocannabinoid palmitoylethanolamide and the synthetic cannabinoid

- nabilone in a model of acute inflammation in the rat. *Br J Pharmacol* 135:181-187, 2002
143. Eberlein B, Eicke C, Reinhardt HW, et al: Adjuvant treatment of atopic eczema: Assessment of an emollient containing N-palmitoylethanolamine (ATOPA study). *J Eur Acad Dermatol Venereol* 22:73-82, 2008
 144. Buddenkotte J, Steinhoff M: Pathophysiology and therapy of pruritus in allergic and atopic diseases. *Allergy* 65:805-821, 2010
 145. Thestrup-Pedersen K: Clinical aspects of glucocorticoid treatment, in Reitamo S (ed): *Textbook of Atopic Dermatitis*. London, Informa Healthcare, 2008, 182
 146. Schmitt J, Schäkel K, Schmitt N, et al: Systemic treatment of severe atopic eczema: A systematic review. *Acta Dermatol Venereol* 87:100-111, 2007
 147. Heddle RJ, Soothill JF, Bulpitt CJ, et al: Combined oral and nasal beclomethasone dipropionate in children with atopic eczema: A randomized controlled trial. *Br Med J (Clin Res Ed)* 289:651-654, 1984
 148. La Rosa M, Musarra I, Ranno C, et al: A randomized, double-blind, placebo-controlled crossover trial for systemic flunisolide in the treatment of children with severe atopic dermatitis. *Curr. Ther Res* 56:720-726, 1995
 149. Eichenfield LF, Hanifin JM, Luger TA, et al: Consensus conference on pediatric atopic dermatitis. *J Am Acad Dermatol* 49:1088-1095, 2003
 150. Wahlgren CF, Scheynius A, Hägermark O: Antipruritic effect of oral cyclosporin A in atopic dermatitis. *Acta Derm Venereol* 70:323-329, 1990
 151. Darsow U, Scharein E, Bromm B, et al: Skin testing of the pruritogenic activity of histamine and cytokines (interleukin-2 and tumour necrosis factor- α) at the dermal-epidermal junction. *Br J Dermatol* 137:415-417, 1997
 152. Sowden JM, Berth-Jones J, Ross JS, et al: Double-blind, controlled, crossover study of cyclosporin in adults with severe refractory atopic dermatitis. *Lancet* 338:137-140, 1991
 153. Atakan N, Erdem C: The efficacy, tolerability and safety of a new oral formulation of Sandimmun--Sandimmun Neoral in severe refractory atopic dermatitis. *J Eur Acad Dermatol Venereol* 11:240-246, 1998
 154. Bunikowski R, Staab D, Kussebi F, et al: Low-dose cyclosporin A microemulsion in children with severe atopic dermatitis: Clinical and immunological effects. *Pediatr Allergy Immunol* 12:216-223, 2001
 155. Schmitt J, Schmitt N, Meurer M: Cyclosporin in the treatment of patients with atopic eczema—A systematic review and meta-analysis. *J Eur Acad Dermatol Venereol* 21:606-619, 2007
 156. Madan V, Griffiths CE: Systemic cyclosporin and tacrolimus in dermatology. *Dermatol Ther* 20:239-250, 2007
 157. Berth-Jones J, Takwale A, Tan E, et al: Azathioprine in severe adult atopic dermatitis: A double-blind, placebo-controlled, crossover trial. *Br J Dermatol* 147:324-330, 2002
 158. Goujon C, Bérard F, Dahel K, et al: Methotrexate for the treatment of adult atopic dermatitis. *Eur J Dermatol* 16:155-158, 2006
 159. Grundmann-Kollmann M, Poddá M, Ochsendorf F, et al: Mycophenolate mofetil is effective in the treatment of atopic dermatitis. *Arch Dermatol* 137:870-873, 2001
 160. Jacobi A, Antoni C, Manger B, et al: Infliximab in the treatment of moderate to severe atopic dermatitis. *J Am Acad Dermatol* 52:522-526, 2005
 161. Stevens SR, Hanifin JM, Hamilton T, et al: Long-term effectiveness and safety of recombinant human interferon gamma therapy for atopic dermatitis despite unchanged serum IgE levels. *Arch Dermatol* 134:799-804, 1998
 162. Ricci G, Dondi A, Patrizi A, et al: Systemic therapy of atopic dermatitis in children. *Drugs* 69:297-306, 2009
 163. Akhavan A, Rudikoff D: Atopic dermatitis: Systemic immunosuppressive therapy. *Semin Cutan Med Surg* 27:151-155, 2008
 164. Buka RL, Resh B, Roberts B, et al: Etanercept is minimally effective in 2 children with atopic dermatitis. *J Am Acad Dermatol* 53:358-359, 2005
 165. Wright RC: Atopic dermatitis-like eruption precipitated by infliximab. *J Am Acad Dermatol* 49:160-161, 2003
 166. Heil PM, Maurer D, Klein B, et al: Omalizumab therapy in atopic dermatitis: Depletion of IgE does not improve the clinical course—A randomized, placebo-controlled and double blind pilot study. *J Dtsch Dermatol Ges* 8:990-998, 2010
 167. Oldhoff JM, Darsow U, Werfel T, et al: Anti-IL-5 recombinant humanized monoclonal antibody (mepolizumab) for the treatment of atopic dermatitis. *Allergy* 60:693-696, 2005
 168. Sedivá A, Kayserová J, Vernerová E, et al: Anti-CD20 (rituximab) treatment for atopic eczema. *J Allergy Clin Immunol* 121:1515-1516, 2008
 169. Radenhausen M, von Kobyletzki G, Höxtermann S, et al: Activation markers in severe atopic dermatitis following extracorporeal photopheresis. *Acta Derm Venereol* 83:49-50, 2003
 170. Kasperkiewicz M, Schmidt E, Frambach Y, et al: Improvement of treatment-refractory atopic dermatitis by immunoadsorption: A pilot study. *J Allergy Clin Immunol* 127:267-270, 2011
 171. Lewis T: *The Blood Vessels of the Human Skin and Their Responses*. London, Shaw and Sons, 1927
 172. Rukwied R, Lischetzki G, McGlone F, et al: Mast cell mediators other than histamine induce pruritus in atopic dermatitis patients: A dermal microdialysis study. *Br J Dermatol* 142:1114-1120, 2000
 173. Heyer G, Hornstein OP, Handwerker HO: Skin reactions and itch sensation induced by epicutaneous histamine application in atopic dermatitis and controls. *J Invest Dermatol* 93:492-496, 1989
 174. Uehara M: Reduced histamine reaction in atopic dermatitis. *Arch Dermatol* 118:244-245, 1982
 175. Klein PA, Clark RA: An evidence-based review of the efficacy of antihistamines in relieving pruritus in atopic dermatitis. *Arch Dermatol* 135:1522-1525, 1999
 176. Ständer S, Schmelz M: Chronic itch and pain—Similarities and differences. *Eur J Pain* 10:473-478, 2006
 177. Hägermark O: Peripheral and central mediators of itch. *Skin Pharmacol* 5:1-8, 1992
 178. Ko MC, Naughton NN: An experimental itch model in monkeys: Characterization of intrathecal morphine-induced scratching and antinociception. *Anesthesiology* 92:795-805, 2000
 179. Bigliardi PL, Bigliardi-Qi M, Buechner S, et al: Expression of mu-opiate receptor in human epidermis and keratinocytes. *J Invest Dermatol* 111, 1998:297-301
 180. Ständer S, Gunzer M, Metzke D, et al: Localization of mu-opioid receptor 1A on sensory nerve fibers in human skin. *Regul Pept* 110, 2002:75-83
 181. Phan NQ, Bernhard JD, Luger TA, et al: Antipruritic treatment with systemic μ -opioid receptor antagonists: A review. *J Am Acad Dermatol* 63:680-688, 2010
 182. Monroe EW: Efficacy and safety of nalmefene in patients with severe pruritus caused by chronic urticaria and atopic dermatitis. *J Am Acad Dermatol* 21:135-136, 1989
 183. Burch JR, Harrison PV: Opiates, sleep and itch. *Clin Exp Dermatol* 13:418-419, 1988
 184. Metzke D, Reimann S, Beissert S, et al: Efficacy and safety of naltrexone, an oral opiate receptor antagonist, in the treatment of pruritus in internal and dermatological diseases. *J Am Acad Dermatol* 41:533-539, 1999
 185. Malekzad F, Arbabi M, Mohtasham N, et al: Efficacy of oral naltrexone on pruritus in atopic eczema: A double-blind, placebo-controlled study. *J Eur Acad Dermatol Venereol* 23:948-950, 2009
 186. Sullivan JR, Watson A: Naltrexone: A case report of pruritus from an antipruritic. *Australas J Dermatol* 38:196-198, 1997
 187. Bergasa NV, Schmitt JM, Talbot TL, et al: Open-label trial of oral nalmefene therapy for the pruritus of cholestasis. *Hepatology* 27:679-684, 1998
 188. Dawn AG, Yosipovitch G: Butorphanol for treatment of intractable pruritus. *J Am Acad Dermatol* 54:527-531, 2006
 189. Kumagai H, Ebata T, Takamori K, et al: Effect of a novel kappa-receptor agonist, nalfurafine hydrochloride, on severe itch in 337 haemodialysis patients: A phase III, randomized, double-blind, placebo-controlled study. *Nephrol Dial Transplant* 25:1251-1257, 2010
 190. Hundley JL, Yosipovitch G: Mirtazapine for reducing nocturnal itch in

- patients with chronic pruritus: A pilot study. *J Am Acad Dermatol* 50:889-891, 2004
191. Ständer S, Böckenholt B, Schürmeyer-Horst F, et al: 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* 89:45-51, 2009
 192. Ständer S, Siepmann D, Herrgott I, et al: Targeting the neurokinin receptor 1 with aprepitant: A novel antipruritic strategy. *PLoS ONE* 5:e10968, 2010
 193. Booken N, Heck M, Nicolay JP, et al: Oral aprepitant in the therapy of refractory pruritus in erythrodermic cutaneous T-cell lymphoma. *Br J Dermatol* 164:665-667, 2011
 194. Rivard J, Lim HW: Ultraviolet phototherapy for pruritus. *Dermatol Ther* 18:344-354, 2005
 195. Wallengren J, Sundler F: Phototherapy reduces the number of epidermal and CGRP-positive dermal nerve fibres. *Acta Derm Venereol* 84: 111-115, 2004
 196. Grabbe J, Welker P, Humke S, et al: High-dose ultraviolet A1 (UVA1), but not UVA/UVB therapy, decreases IgE-binding cells in lesional skin of patients with atopic eczema. *J Invest Dermatol* 107:419-422, 1996
 197. Piletta PA, Wirth S, Hommel L, et al: Circulating skin-homing T cells in atopic dermatitis. Selective up-regulation of HLA-DR, interleukin-2R, and CD30 and decrease after combined UV-A and UV-B phototherapy. *Arch Dermatol* 132:1171-1177, 1996
 198. Jekler J, Larkö O: UVB phototherapy of atopic dermatitis. *Br J Dermatol* 119:697-705, 1988
 199. Clayton TH, Clark SM, Turner D, et al: The treatment of severe atopic dermatitis in childhood with narrowband ultraviolet B phototherapy. *Clin Exp Dermatol* 32:28-33, 2007
 200. Jekler J, Larkö O: UVA-UVB versus UVB phototherapy for atopic dermatitis: A paired-comparison study. *J Am Acad Dermatol* 22:49-53, 1990
 201. von Kobyletzki G, Pieck C, Hoffmann K, et al: Medium-dose UVA1 cold-light phototherapy in the treatment of severe atopic dermatitis. *J Am Acad Dermatol* 41:931-937, 1999
 202. Reynolds NJ, Franklin V, Gray JC, et al: Narrow-band ultraviolet B and broad-band ultraviolet A phototherapy in adult atopic eczema: A randomised controlled trial. *Lancet* 357:2012-2016, 2001
 203. Krutmann J, Diepgen TL, Luger TA, et al: High-dose UVA1 therapy for atopic dermatitis: Results of a multicenter trial. *J Am Acad Dermatol* 38:589-593, 1998
 204. Sheehan MP, Atherton DJ, Norris P, et al: Oral psoralen photochemotherapy in severe childhood atopic eczema: An update. *Br J Dermatol* 129:431-436, 1993
 205. Uetsu N, Horio T: Treatment of persistent severe atopic dermatitis in 113 Japanese patients with oral psoralen photo-chemotherapy. *J Dermatol* 30:450-457, 2003
 206. Der-Petrosian M, Seeber A, Hönigsman H, et al: 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* 142:39-43, 2000
 207. Baltás E, Csoma Z, Bodai L, et al: Treatment of atopic dermatitis with the xenon chloride excimer laser. *J Eur Acad Dermatol Venereol* 20: 657-660, 2006
 208. Nisticò SP, Saraceno R, Capriotti E, et al: Efficacy of monochromatic excimer light (308 nm) in the treatment of atopic dermatitis in adults and children. *Photomed Laser Surg* 26:14-18, 2008
 209. Brenninkmeijer EE, Spuls PI, Lindeboom R, et al: Excimer laser vs. clobetasol propionate 0.05% ointment in prurigo form of atopic dermatitis: A randomized controlled trial, a pilot. *Br J Dermatol* 163:823-831, 2010
 210. Goeckerman WH: The treatment of psoriasis. *Northwest Med* 24:229-231, 1925
 211. Kortuem KR, Davis MD, Witman PM, et al: Results of Goeckerman treatment for psoriasis in children: A 21-year retrospective review. *Pediatr Dermatol* 27:518-524, 2010
 212. Lee E, Koo J: Modern modified "ultra" Goeckerman therapy: A Pasi assessment of a very effective therapy for psoriasis resistant to both prebiologic and biologic therapies. *J Dermatol Treat* 16:102-107, 2005
 213. Lee E, Koo J, Berger T: UVB phototherapy and skin cancer risk: A review of the literature. *Int J Dermatol* 44:355-360, 2005
 214. Stern RS, Laird N: The carcinogenic risk of treatments for severe psoriasis. *Photochemotherapy Follow-up Study. Cancer* 73:2759-2764, 1994
 215. Lim JL, Stern RS: High levels of ultraviolet B exposure increase the risk of non-melanoma skin cancer in psoralen and ultraviolet A-treated patients. *J Invest Dermatol* 124, 2005:505-513
 216. Hearn RM, Kerr AC, Rahim KF, et al: Incidence of skin cancers in 3867 patients treated with narrow-band ultraviolet B phototherapy. *Br J Dermatol* 159:931, 2008
 217. Patel RV, Clark LN, Leibold M, et al: Treatments for psoriasis and the risk of malignancy. *J Am Acad Dermatol* 60:1001-1017, 2009
 218. Lindelöf B, Sigurgeirsson B, Tegner E, et al: PUVA and cancer risk: The Swedish Follow-Up study. *Br J Dermatol* 141:108-112, 1999
 219. Stern RS, Leibman EJ, Vakeva L: Oral psoralen and ultraviolet-A light (PUVA) treatment of psoriasis and persistent risk of nonmelanoma skin cancer. *J Natl Cancer Inst* 90, 1998:1278-1284
 220. Stern RS, Khahn NT, Vakeva LH: Malignant melanoma in patients treated for psoriasis with methoxsalen (Psoralen) and ultraviolet A radiation (PUVA). *N Engl J Med* 336, 1997:1041-1045
 221. Stern RS: The risk of melanoma in association with long-term exposure to PUVA. *J Am Acad Dermatol* 44:755-761, 2001
 222. Bartlett EE, Hutserani O: Xylocaine for the relief of postoperative pain. *Anesth Analg* 40:296-304, 1961
 223. Mao J, Chen LL: Systemic lidocaine for neuropathic pain relief. *Pain* 87:7-17, 2000
 224. Boas RA, Covino BG, Shahnarian A: Analgesic responses to i.v. lignocaine. *Br J Anaesth* 54:501-505, 1982
 225. Villamil AG, Bandi JC, Galdame OA, et al: Efficacy of lidocaine in the treatment of pruritus in patients with chronic cholestatic liver diseases. *Am J Med* 118:1160-1163, 2005
 226. Dey DD, Landrum O, Oaklander AL: Central neuropathic itch from spinal-cord cavernous hemangioma: A human case, a possible animal model, and hypotheses about pathogenesis. *Pain* 113:233-237, 2005
 227. Sandroni P: Central neuropathic itch: A new treatment option? *Neurology* 59:778-779, 2002
 228. Freeman CW: A new topical remedy useful in the management of pruritus. *J Natl Med Assoc* 53:151-153, 1961
 229. Inan S, Dun NJ, 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* 616:141-146, 2009
 230. Sheehan MP, Rustin MH, Atherton DJ, et al: Efficacy of traditional Chinese herbal therapy in adult atopic dermatitis. *Lancet* 340:13-17, 1992
 231. Fung AY, Look PC, Chong LY, et al: A controlled trial of traditional Chinese herbal medicine in Chinese patients with recalcitrant atopic dermatitis. *Int J Dermatol* 38:387-392, 1999
 232. Latchman Y, Bungy GA, Atherton DJ, et al: Efficacy of traditional Chinese herbal therapy in vitro. A model system for atopic eczema: Inhibition of CD23 expression on blood monocytes. *Br J Dermatol* 132:592-598, 1995
 233. Cheng HM, Chiang LC, Jan YM, et al: The efficacy and safety of a Chinese herbal product (Xiao-Feng-San) for the treatment of refractory atopic dermatitis: a randomized, double-blind, placebo-controlled trial. *Int Arch Allergy Immunol* 155:141-148, 2010
 234. Reuter J, Wölfe U, Weckesser S, et al: Which plant for which skin disease? part 1: Atopic dermatitis, psoriasis, acne, condyloma and herpes simplex. *J Dtsch Dermatol Ges* 8:788-796, 2010
 235. Schempp CM, Hezel S, Simon JC: Topical treatment of atopic dermatitis with Hypericum cream. A randomised, placebo-controlled, double-blind halfside comparison study. *Hautarzt* 54:248-253, 2003
 236. Saedi M, Morteza-Semnani K, Ghoreishi MR: The treatment of atopic dermatitis with licorice gel. *J Dermatol Treat* 14:153-157, 2003
 237. Donsky H, Clarke D: Reliëva, a Mahonia aquifolium extract for the

- treatment of adult patients with atopic dermatitis. *Am J Ther* 14:442-446, 2007
238. Sokel B, Kent CA, Lansdown R, et al: A comparison of hypnotherapy and biofeedback in the treatment of childhood atopic eczema. *Contemp Hypn* 10:145-154, 1993
 239. Schachner L, Field T, Hernandez-Reif M, et al: Atopic dermatitis symptoms decreased in children following massage therapy. *Pediatr Dermatol* 15:390-395, 1998
 240. Stewart AC, Thomas SE: Hypnotherapy as a treatment for atopic dermatitis in adults and children. *Br J Dermatol* 132:778-783, 1995
 241. Fjellner B, Arnetz BB: Psychological predictors of pruritus during mental stress. *Acta Derm Venereol* 65:504-508, 1985
 242. Gupta MA, Gupta AK, Schork NJ, et al: Depression modulates pruritus perception: A study of pruritus in psoriasis, atopic dermatitis, and chronic idiopathic urticaria. *Psychosom Med* 56:36-40, 1994
 243. Homey B, Steinhoff M, Ruzicka T, et al: Cytokines and chemokines orchestrate atopic skin inflammation. *J Allergy Clin Immunol* 118:178-189, 2006
 244. Mahtani R, Perekh N, Mangat I, et al: Alleviating the itch-scratch cycle in atopic dermatitis. *Psychosomatics* 46:373-374, 2005
 245. van Os-Medendorp H, Eland-de Kok PC, Grypdonck M, et al: Prevalence and predictors of psychosocial morbidity in patients with chronic pruritic skin diseases. *J Eur Acad Dermatol Venereol* 20:810-811, 2006
 246. Oh SH, Bae BG, Park CO, et al: Association of stress with symptoms of atopic dermatitis. *Acta Derm Venereol* 90:582-588, 2010
 247. Fjellner B, Arnetz BB, Eneroth P, et al: Pruritus during standardized mental stress. Relationship to psychoneuroendocrine and metabolic parameters. *Acta Derm Venereol* 65:199-205, 1985
 248. Buske-Kirschbaum A, Gierens A, Höllig H, et al: Stress-induced immunomodulation is altered in patients with atopic dermatitis. *J Neuroimmunol* 129:161-167, 2002
 249. Tran BW, Papoiu AD, Russoniello CV, et al: Effect of itch, scratching and mental stress on autonomic nervous system function in atopic dermatitis. *Acta Derm Venereol* 90:354-361, 2010
 250. Habib S, Morrissey S: Stress management for atopic dermatitis. *Behav Change* 16:226-236, 1999
 251. Ehlers A, Stangier U, Gieler U: Treatment of atopic dermatitis: A comparison of psychological and dermatological approaches to relapse prevention. *J Consult Clin Psychol* 63:624-635, 1995
 252. Jordan JM, Whitlock FA: Emotions and the skin: The conditioning of scratch responses in cases of atopic dermatitis. *Br J Dermatol* 86:574-585, 1972
 253. Norén P: Habit reversal: A turning point in the treatment of atopic dermatitis. *Clin Exp Dermatol* 20:2-5, 1995
 254. Norén P, Melin L: The effect of combined topical steroids and habit-reversal treatment in patients with atopic dermatitis. *Br J Dermatol* 121:359-366, 1989
 255. Melin L, Frederiksen T, Noren P, et al: Behavioural treatment of scratching in patients with atopic dermatitis. *Br J Dermatol* 115:467-474, 1986
 256. Chida Y, Steptoe A, Hirakawa N, et al: The effects of psychological intervention on atopic dermatitis. A systematic review and meta-analysis. *Int Arch Allergy Immunol* 144:1-9, 2007
 257. Skellett A, Swift L, Tan E, et al: A randomized, double-blind, negatively controlled pilot study to determine whether the use of emollients or calcipotriol alters the sensitivity of the skin to ultraviolet radiation during phototherapy with narrowband ultraviolet B. *Br J Dermatol* 164:402-406, 2011
 258. Jensen P, Skov L, Zachariae C: Systemic combination treatment for psoriasis: A review. *Acta Derm Venereol* 90:341-349, 2010
 259. Hodari KT, Nanton JR, Carroll CL, et al: Adherence in dermatology: A review of the last 20 years. *J Dermatol Treat* 17:136-142, 2006
 260. Ou HT, Feldman SR, Balkrishnan R: Understanding and improving treatment adherence in pediatric patients. *Semin Cutan Med Surg* 29:137-140, 2010
 261. Cork MJ, Britton J, Butler L, et al: Comparison of parent knowledge, therapy utilization and severity of atopic eczema before and after explanation and demonstration of topical therapies by a specialist dermatology nurse. *Br J Dermatol* 149:582-589, 2003
 262. Basak PY, Ozturk M, Baysal M: Assessment of information and education about topical corticosteroids in dermatology outpatient departments: Experience from Turkey. *J Eur Acad Dermatol Venereol* 17:652-658, 2003
 263. Koehler AM, Maibach HI: Electronic monitoring in medication adherence measurement. Implications for dermatology. *Am J Clin Dermatol* 2:7-12, 2001
 264. Ntuen E, Taylor SL, Kinney M, et al: Physicians' perceptions of an eczema action plan for atopic dermatitis. *J Dermatol Treat* 21:28-33, 2010
 265. Chisolm SS, Taylor SL, Balkrishnan R, et al: Written action plans: Potential for improving outcomes in children with atopic dermatitis. *J Am Acad Dermatol* 59:677-683, 2008
 266. Houts PS, Doak CC, Doak LG, et al: The role of pictures in improving health communication: A review of research on attention, comprehension, recall, and adherence. *Patient Educ Couns* 61:173-190, 2006
 267. Austin PE, Matlack R, Dunn KA, et al: Discharge instructions: Do illustrations help our patients understand them? *Ann Emerg Med* 25:317-320, 1995
 268. van Os-Medendorp H, Ros WJ, Eland-de Kok PC, et al: Effectiveness of the nursing programme "Coping with itch": A randomized controlled study in adults with chronic pruritic skin disease. *Br J Dermatol* 156:1235-1244, 2007
 269. van Os-Medendorp H, Eland-de Kok PC, Grypdonck M, et al: Prevalence and predictors of psychosocial morbidity in patients with chronic pruritic skin diseases. *J Eur Acad Dermatol Venereol* 20:810-817, 2006
 270. Evers AW, Lu Y, Duller P, et al: Common burden of chronic skin diseases? Contributors to psychological distress in adults with psoriasis and atopic dermatitis. *Br J Dermatol* 152:1275-1281, 2005
 271. Staab D, Diepgen TL, Fartasch M, et al: Age related, structured educational programmes for the management of atopic dermatitis in children and adolescents: Multicentre, randomised controlled trial. *BMJ* 332:933-938, 2006
 272. Boguniewicz M, Nicol N, Kelsay K, et al: A multidisciplinary approach to evaluation and treatment of atopic dermatitis. *Semin Cutan Med Surg* 27:115-127, 2008
 273. Kelsay K, Carel D, Bratton DL, et al: Functional status following treatment of children with atopic dermatitis. *J Allergy Clin Immunol* 117:s233, 2006