

Antipruritic treatment

Itch is the most important clinical symptom in AE with particular impact on emotional dimensions of perception as compared to other pruritic dermatoses. Most drugs successfully used in AE patients, because they are targeting the inflammation, will also have a measurable effect on the itch. There is only a limited number of studies that specifically assessed the antipruritic effect of treatment modalities in AE. The treatment of itch in AE requires a multi-dimensional approach treating itch itself, but also the contributing factors, such as the dry skin and skin inflammation.

Anti-pruritic effect of anti-inflammatory treatment

The anti-inflammatory agents, both topical and systemic ones, reduce skin lesions and significantly relieve itch. Although topical corticosteroids do not act as direct antipruritic agents,¹ several studies described the anti-inflammatory effect of topical corticosteroids in AE, in which pruritus was one parameter among others studied.²

Topical calcineurin inhibitors relieve pruritus significantly in AE. Itch is completely relieved after the first days of treatment in both adults and children. Topical calcineurin inhibitors appeared to significantly reduce AE itch by 36% compared to vehicle application.²


Crisaborole was shown to be effective in reducing itch in mild-to-moderate AE patients. Reszke et al. in their review consider that patients receiving crisaborole 2% ointment experienced pruritus relief at day 29 more commonly than patients receiving vehicle.³ Furthermore, crisaborole was more likely to provide antipruritic response at the earliest assessment on day 2 and early improvement of pruritus at day 6 than vehicle.³ However, crisaborole is not available on the European market.

Dupilumab as systemic anti-inflammatory agent showed high effectiveness in reducing itch in AE patients. All the studies confirmed the efficacy of dupilumab in terms of improvement of skin lesions and alleviation of pruritus.⁴⁻⁷ Similar data exists for other systemic drugs recently licensed for AE treatment, such as tralokinumab, abrocitinib, baricitinib and upadacitinib (see chapters Biologics and JAK-Inhibitors).⁸⁻¹¹

A meta-analysis of 1505 patients with moderate-to-severe AE revealed that dupilumab started to unveil its antipruritic properties by days 2 and 5 in adults and adolescents, respectively. The response increased over time and was sustained until the end of the studies (up to 1 year).⁵

Anti-pruriginic treatment

Polidocanol


We cannot make a recommendation on the use of polidocanol in itch treatment in AE.	0	<p style="text-align: center;">>75%</p>  <p style="text-align: center;">(16/17) Expert Consensus</p>
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Case series described the efficacy of a combination of the anaesthetic polidocanol and 5% urea.¹² In children with AE, the combination showed a pruritus improvement of 30% in comparison with an emollient.¹³ Polidocanol is not licensed for AE in Europe, but OTC products are available.

Capsaicin

Capsaicin is a naturally occurring alkaloid and the principal pungent of hot chilli peppers. Capsaicin binds to the TRPV1 ion channel, which is present on many itch-mediating C-fibres. Capsaicin has been advocated to be antipruritic in various dermatoses. Concerning AE, experimental studies¹⁴ and case series¹⁵ report on clear itch reduction. However, the practical treatment and updosing are challenging, and no controlled study has been published.


Topical antihistamines

We recommend against topical antihistamines in itch treatment in AE.	↓↓	<p style="text-align: center;">>75%</p>  <p style="text-align: center;">(17/18)¹ Expert Consensus</p>
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¹ 1 Abstention

5% doxepin cream exhibited antipruritic effects in three controlled studies in AE; one RCT assessed the efficacy of cromoglycate 4% lotion.² The meta-analysis of those studies documented that the use of topical antihistamines markedly reduced itch of AE by 27% in patients in comparison with the vehicle. However, topical doxepin therapy is not licensed and not used in any European country due to an increased risk of contact allergy, especially when the treatment exceeds eight days.


UV therapy


<p>We suggest UV therapy (both narrowband UVB and UVA1) for the treatment of itch in AE.</p> <p>Also see phototherapy chapter</p>	↑	<p style="text-align: center;">>75%</p>  <p style="text-align: center;">(17/19)¹ Expert Consensus</p>
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¹2 Abstention

UV phototherapy relieves pruritus in AE, which has been demonstrated in several studies. A systematic review of 19 available RCTs suggests the usage of narrowband UVB and UVA1 as the most effective in the treatment of AE, including reduction in itch intensity.¹⁶ A recent study by Jaworek et al.¹⁷ documented that narrowband UVB reduces itch in AE patients significantly better than ciclosporine.¹⁷ There is no 'anti-itch-specific' data for UV phototherapy available, which would differ from the general recommendations for UV phototherapy treatment of AE.

Systemic antihistamines

<p>We suggest against using first generation systemic antihistamines as a longterm treatment for itch in AE.</p>	↓	<p style="text-align: center;">100%</p>  <p style="text-align: center;">100 % Agreement</p> <p style="text-align: center;">(22/22) Expert Consensus</p>
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<p>We suggest against using second generation systemic antihistamines as a treatment for itch in AE.</p>	↓	<p style="text-align: center;">>75%</p>  <p style="text-align: center;">(13/15)¹ Expert Consensus</p>
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¹ 1 Abstention


Antihistamines (AH) have been used for decades in an attempt to relieve pruritus in patients with AE. However, only a few randomized controlled trials have been conducted and the majority of them showed only a weak or no effect in decreasing pruritus.¹⁸⁻²⁶ A recent Cochrane review did not find consistent evidence that H1 AH treatments are effective as 'add-on' therapy for AE when compared to placebo.²⁷ The certainty of evidence for this comparison was of low and moderate quality.²⁷ It seems that only fexofenadine may lead to small improvement in patient-assessed pruritus (mean difference (MD) -0.25, 95% CI -0.43 to -0.07; n = 400) and a greater reduction in the ratio of physician-assessed pruritus area to whole body surface area.^{27, 28} However, these reductions may not be clinically meaningful²⁷. In general, AH are safe to use, also for a long period of time.²⁹ There is limited data for the antipruritic effect of AH (H1 antagonists) in AE in general, and the effect of both first and second generation AH on pruritus in patients suffering from AE is very limited. The clinical value of systemic antihistamines for the anti-pruritic treatment of AE is not supported.

Especially the first generation of systemic AH may affect sleep quality and reduce rapid eye movement (REM)-sleep. Therefore, regular long-term use of sedating antihistamines is not recommended.³⁰⁻³²

Opioid receptor antagonists

The μ -opioid receptor antagonist nalmefene was applied in smaller randomized, controlled studies in AE. A dosage of 10 and 20 mg each once per day showed significant relief of pruritus in three studies.³³⁻³⁵ In open-label trials and one double-blind, placebo-controlled study trial, the only orally active μ -opioid antagonist naltrexone 25–150 mg per day showed considerable antipruritic effects.^{36, 37} Common adverse events include anxiety, arthralgia, dizziness, drowsiness, fatigue, vomiting and headache. None of these substances is currently licensed for the treatment of AE itch. The benefit-risk ratio is unfavourable.

Selective serotonin reuptake inhibitors

<p>We suggest against the use of selective serotonin reuptake inhibitors as itch treatment in AE patients.</p>	<p>↓</p>	<p>100%</p>  <p>100 % Agreement</p> <p>(20/20) Expert Consensus</p>
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The antipruritic effect of the selective serotonin reuptake inhibitors paroxetine and fluvoxamine was investigated in an open-label trial in dermatological patients. A few patients with pruritus due to AE were included, who responded with considerable reduction in pruritus. In these patients, the pruritus was reduced about half in intensity (maximal antipruritic effect score, $45.0 \pm 7.1\%$).³⁸ Although the evidence of antipruritic activity of selective serotonin reuptake inhibitors in AE is very low, these agents might be used as second or third line therapy in other types of chronic itch.

Adverse events include constipation, diarrhoea, dizziness, drowsiness, ejaculatory and erectile dysfunction, decreased libido, insomnia, nausea and headache. The risk–benefit ratio of SSRI is highly unfavourable.

References

- [1] Kamata Y, Tominaga M, Takamori K. Itch in Atopic Dermatitis Management. *Curr Probl Dermatol.* 2016;50; 86-93.
- [2] Sher LG, Chang J, Patel IB, Balkrishnan R, Fleischer AB, Jr. Relieving the pruritus of atopic dermatitis: a meta-analysis. *Acta Derm Venereol.* 2012;92; 455-461.
- [3] Reszke R, Krajewski P, Szepietowski JC. Emerging Therapeutic Options for Chronic Pruritus. *American journal of clinical dermatology.* 2020;21; 601-618.
- [4] Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. *N Engl J Med.* 2016;375; 2335-2348.
- [5] Silverberg JI, Yosipovitch G, Simpson EL, Kim BS, Wu JJ, Eckert L, et al. Dupilumab treatment results in early and sustained improvements in itch in adolescents and adults with moderate to severe atopic dermatitis: Analysis of the randomized phase 3 studies SOLO 1 and SOLO 2, AD ADOL, and CHRONOS. *Journal of the American Academy of Dermatology.* 2020;82; 1328-1336.
- [6] Agache I, Song Y, Posso M, Alonso-Coello P, Rocha C, Solà I, et al. Efficacy and safety of dupilumab for moderate-to-severe atopic dermatitis: A systematic review for the EAACI biologicals guidelines. *Allergy.* 2021;76; 45-58.
- [7] Worm M, Simpson EL, Thaçi D, Bissonnette R, Lacour JP, Beissert S, et al. Efficacy and Safety of Multiple Dupilumab Dose Regimens After Initial Successful Treatment in Patients With Atopic Dermatitis: A Randomized Clinical Trial. *JAMA Dermatol.* 2020;156; 131-143.
- [8] Wollenberg A, Blauvelt A, Guttman-Yassky E, Worm M, Lynde C, Lacour JP, et al. Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). *Br J Dermatol.* 2021;184; 437-449.
- [9] Simpson EL, Sinclair R, Forman S, Wollenberg A, Aschoff R, Cork M, et al. Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet.* 2020;396; 255-266.
- [10] Simpson EL, Lacour JP, Spelman L, Galimberti R, Eichenfield LF, Bissonnette R, et al. Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. *Br J Dermatol.* 2020;183; 242-255.
- [11] Guttman-Yassky E, Teixeira HD, Simpson EL, Papp KA, Pangan AL, Blauvelt A, et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. *Lancet.* 2021;397; 2151-2168.
- [12] Schommer A, Matthies C, Petersen I, Augustin M. Effektivität einer Polidocanol-Harnstoff-Kombination bei trockener, juckender Haut. *Aktuelle Dermatologie.* 2007;33; 33-38.
- [13] Hauss H, Proppe A, Matthies C. Vergleichende Untersuchungen zur Behandlung von trockener, juckender Haut mit einer Zubereitung aus Harnstoff und Polidocanol sowie mit einer Linolsäure-haltigen Fettcreme. *Ergebnisse aus der Praxis. Derm Beruf Umwelt.* 1993;41; 184-188.
- [14] Weisshaar E, Heyer G, Forster C, Handwerker HO. Effect of topical capsaicin on the cutaneous reactions and itching to histamine in atopic eczema compared to healthy skin. *Arch Dermatol Res.* 1998;290; 306-311.
- [15] Reimann S, Luger T, Metze D. [Topical administration of capsaicin in dermatology for treatment of itching and pain]. *Hautarzt.* 2000;51; 164-172.
- [16] Garritsen FM, Brouwer MW, Limpens J, Spuls PI. Photo(chemo)therapy in the management of atopic dermatitis: an updated systematic review with implications for practice and research. *Br J Dermatol.* 2014;170; 501-513.
- [17] Jaworek A, Szafraniec K, Jaworek M, Matusiak Ł, Wojas-Pelc A, Szepietowski JC. Itch Relief in Atopic Dermatitis: Comparison of Narrowband Ultraviolet B Radiation and Cyclosporine Treatment. *Acta Derm Venereol.* 2020;100; adv00291.

- [18] Doherty V, Sylvester DG, Kennedy CT, Harvey SG, Calthrop JG, Gibson JR. Treatment of itching in atopic eczema with antihistamines with a low sedative profile. *Bmj*. 1989;298; 96.
- [19] Henz BM, Metzenauer P, O'Keefe E, Zuberbier T. Differential effects of new-generation H1-receptor antagonists in pruritic dermatoses. *Allergy*. 1998;53; 180-183.
- [20] Langeland T, Fagertun HE, Larsen S. Therapeutic effect of loratadine on pruritus in patients with atopic dermatitis. A multi-crossover-designed study. *Allergy*. 1994;49; 22-26.
- [21] La Rosa M, Ranno C, Musarra I, Guglielmo F, Corrias A, Bellanti JA. Double-blind study of cetirizine in atopic eczema in children. *Ann Allergy*. 1994;73; 117-122.
- [22] Wahlgren CF, Hägermark O, Bergström R. The antipruritic effect of a sedative and a non-sedative antihistamine in atopic dermatitis. *Br J Dermatol*. 1990;122; 545-551.
- [23] Munday J, Bloomfield R, Goldman M, Robey H, Kitowska GJ, Gwiedzinski Z, et al. Chlorpheniramine is no more effective than placebo in relieving the symptoms of childhood atopic dermatitis with a nocturnal itching and scratching component. *Dermatology*. 2002;205; 40-45.
- [24] Hannuksela M, Kalimo K, Lammintausta K, Mattila T, Turjanmaa K, Varjonen E, et al. Dose ranging study: cetirizine in the treatment of atopic dermatitis in adults. *Ann Allergy*. 1993;70; 127-133.
- [25] Chunharas A, Wisuthsarewong W, Wananukul S, Viravan S. Therapeutic efficacy and safety of loratadine syrup in childhood atopic dermatitis treated with mometasone furoate 0.1 per cent cream. *J Med Assoc Thai*. 2002;85; 482-487.
- [26] Kawakami T, Kaminishi K, Soma Y, Kushimoto T, Mizoguchi M. Oral antihistamine therapy influences plasma tryptase levels in adult atopic dermatitis. *J Dermatol Sci*. 2006;43; 127-134.
- [27] Matteredne U, Böhmer MM, Weisshaar E, Jupiter A, Carter B, Apfelbacher CJ. Oral H1 antihistamines as 'add-on' therapy to topical treatment for eczema. *Cochrane Database Syst Rev*. 2019;1; Cd012167.
- [28] Kawashima M, Tango T, Noguchi T, Inagi M, Nakagawa H, Harada S. Addition of fexofenadine to a topical corticosteroid reduces the pruritus associated with atopic dermatitis in a 1-week randomized, multicentre, double-blind, placebo-controlled, parallel-group study. *Br J Dermatol*. 2003;148; 1212-1221.
- [29] Simons FE. Safety of levocetirizine treatment in young atopic children: An 18-month study. *Pediatr Allergy Immunol*. 2007;18; 535-542.
- [30] Wollenberg A, Christen-Zäch S, Taieb A, Paul C, Thyssen JP, de Bruin-Weller M, et al. ETFAD/EADV Eczema task force 2020 position paper on diagnosis and treatment of atopic dermatitis in adults and children. *J Eur Acad Dermatol Venereol*. 2020;34; 2717-2744.
- [31] Church MK, Maurer M, Simons FE, Bindslev-Jensen C, van Cauwenberge P, Bousquet J, et al. Risk of first-generation H(1)-antihistamines: a GA(2)LEN position paper. *Allergy*. 2010;65; 459-466.
- [32] Adam K, Oswald I. The hypnotic effects of an antihistamine: promethazine. *Br J Clin Pharmacol*. 1986;22; 715-717.
- [33] Monroe EW. Efficacy and safety of nalmefene in patients with severe pruritus caused by chronic urticaria and atopic dermatitis. *Journal of the American Academy of Dermatology*. 1989;21; 135-136.
- [34] Burch JR, Harrison PV. Opiates, sleep and itch. *Clin Exp Dermatol*. 1988;13; 418-419.
- [35] Banerji D, Fox R, Seleznick M, Lockey R. 337 Controlled antipruritic trial of nalmefene (N) in chronic urticaria (CU) and atopic dermatitis (AD). *Journal of Allergy and Clinical Immunology*. 1988;81; 252.
- [36] Metze D, Reimann S, Beissert S, Luger T. Efficacy and safety of naltrexone, an oral opiate receptor antagonist, in the treatment of pruritus in internal and dermatological diseases. *Journal of the American Academy of Dermatology*. 1999;41; 533-539.
- [37] Malekzad F, Arbabi M, Mohtasham N, Toosi P, Jaberian M, Mohajer M, et al. Efficacy of oral naltrexone on pruritus in atopic eczema: a double-blind, placebo-controlled study. *J Eur Acad Dermatol Venereol*. 2009;23; 948-950.

[38] Ständer S, Böckenholt B, Schürmeyer-Horst F, Weishaupt C, Heuft G, Luger TA, 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.* 2009;89; 45-51.