

REVIEW

Characteristics, mechanism, and management of pain in atopic dermatitis: A literature review

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Funding information

National Natural Science Foundation of China, Grant/Award Number: 81602765

Abstract

Background: Atopic dermatitis (AD) is a chronic, pruritic, immune-mediated inflammatory disease. Developments in basic science and clinical research have increased our understanding of AD. Although pain as a symptom of AD is under-emphasized in previous studies, multiple researchers address pain as a frequent burden of AD. However, the exact role of pain in AD is not fully understood.

Aims: Our review aimed to summarize the current evidence focusing on characteristics, mechanism, and management of pain in AD.

Materials & Methods: We conducted a thorough literature review in the PubMed database to figure out different aspects discussing pain in AD, including pain symptoms, burden, the relationship between pain and itch, mechanism, and pain management in AD.

Results and Conclusion: AD patients affected by skin pain vary from 42.7%-92.2% with remarkable intensity and heavy burden. Skin pain and itch interacted both in symptoms and mechanisms. Atopic skin with the impaired barrier, neurogenic inflammation mediators, peripheral and central sensitization of pain may possibly explain pain mechanism in AD. Future research is needed to clarify the commonality and disparity of pain and itch in AD in order to seek efficacious medications and treatment.

KEYWORDS

atopic dermatitis, epidemiology, management, mechanism, pain

MOTS-CLÉS

atopische dermatitis, épidémiologie, management, mécanisme, schmerzen

1 | INTRODUCTION

Atopic dermatitis (AD) is one of the most common chronic skin diseases and is characterized by itch and inflammatory eczematous lesions. This condition not only affects children (20%) but also is

prevalent in adults (10%), especially in developed countries.¹ Impairment in physical or psychosocial activities is caused by AD, resulting in, for example, sleep disturbances, depression, or anxiety, all of which place an enormous economic burden on health resources.² Epidermal barrier disruptions and skin inflammation

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mutually reinforce AD pathophysiological processes. A consequence of the interaction of a compromised barrier with the type 2 immune environment is the promotion of percutaneous allergic sensitization.³ In addition, AD may increase the risk of asthma, allergic rhinitis, or other immune-mediated inflammatory diseases. Although itch is the most prominent symptom, pain has recently been considered a nonnegligible burden for AD.⁴

As defined by Samuel Hafrenreffer, itch is an unpleasant sensation associated with the desire or reflex to scratch. The definition of pain promulgated by the international association is that pain is a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive, and social components.⁵

A thorough search of the literature was performed in the PubMed database using (atopic dermatitis OR eczema) AND (pain) as search terms. There was an obvious increase from 147 articles before 2000 to 808 articles until 2021, reflecting aroused interest in clinical practice. After adding “clinical study” as the article type, 86 articles were found, and finally, we included 3 original articles related to pain in AD. The rules for excluding irrelevant publications were AD without pain description or pain symptoms with other types of dermatitis. Additional articles were retrieved through the hand-searching of reference lists.

2 | EPIDEMIOLOGY OF AD

The prevalence of AD is increasing,⁶ and the prevalence and severity of the disease vary in different regions and ethnic populations.^{7,8} In particular, 10.7%–20% children currently suffer from AD.^{8–10} The prevalence of adult AD was reported to be 4.9% in the United States, 3.5% in Canada, 4.4% in the EU, 2.1%–6.9% in Japan, and 2.6% in Korea, ranging from 2.6%–6.9% worldwide.^{11–13}

Although AD is usually characterized as a childhood disease, persistence of AD from children to adults is common, particularly in those with early onset in infancy.¹⁴ With a 34.1% lifetime prevalence of AD, nearly half (10%–17.1%) of AD adults continuously suffered from a schooltime age diagnosis of AD, as reported in a Denmark prospective study.¹⁵ Although child-onset AD is more prevalent, adult-onset AD is not uncommon, noted as 11%–13% in some countries.¹⁶

3 | PAIN IS A COMMON SYMPTOM IN AD

Although itch is the predominant and most common feature of AD, the symptom of pain is emphasized as more frequently encountered than perceived. However, pain symptoms, unlike itch, have not been assessed thoroughly. Sometimes, itch and pain appear at the same time, making it hard to distinguish their respective impacts. However, half of the AD patients (50.4%) in one study were able to distinguish between the two symptoms.¹⁷ A total of 59%–78% of AD patients have been reported to present with undistinguished and accompanied pain and itch.^{18,19}

Various evaluations of itch in AD patients are applied in practice; however, pain is often inadequately estimated.²⁰ Although few

studies have paid attention to pain symptom in the past, to update the findings, skin pain is commonly experienced by a great proportion of AD patients, ranging from 42.7% to 92.2%.^{17,21–24} The McGill questionnaire is used to evaluate pain from five different dimensions.²⁴ Greater pain burden usually occurred on the hands, perioral regions, plantar and toes, neck, and chest, where the cutaneous sensory nerve distribution is denser (Figure 1).^{18,25}

Considering the description of skin pain among AD patients, burning (71.4%) was the most commonly used descriptor, followed by prickling (65.2%). Additionally, tingling (25.6%), electric shock sensation (25.6%), and cold pain sensation (14.3%) were less likely to be experienced.²² A recent survey by Pojawa-Gołąb and Reich provided similar results, showing that most AD patients (77.2%) complained about burning/stinging pain, and a great amount of them (60.7%) considered this pain annoying. Some AD patients (29.4%) described it as a sharp pain.¹⁷

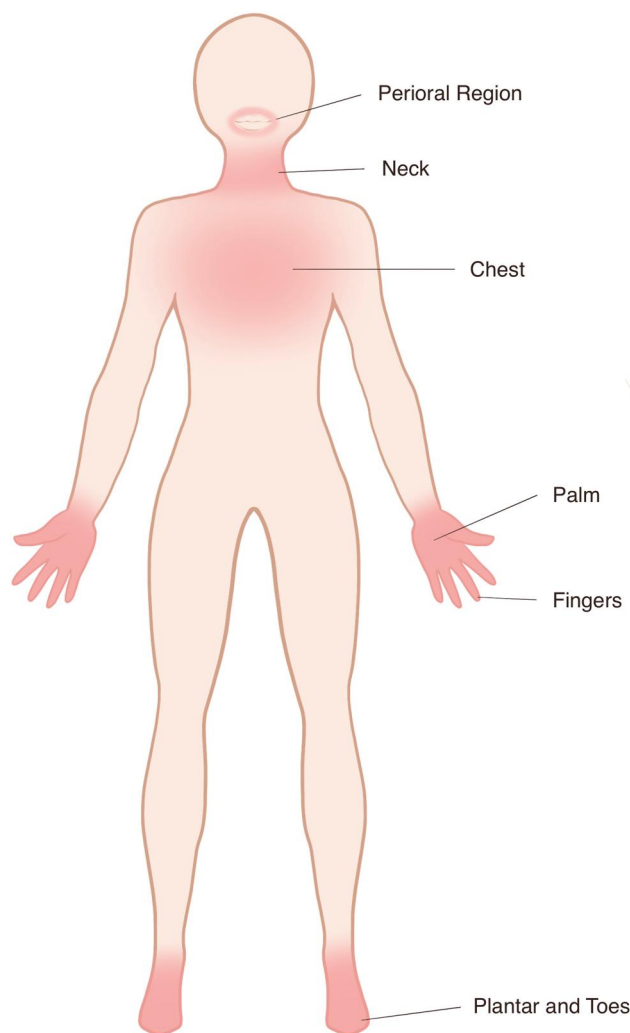


FIGURE 1 Areas with greater pain burden. The greater pain burdens usually occur on the hands, perioral regions, plantar and toes, neck, and chest where cutaneous sensory nerve distribution is denser

To characterize the frequency, intensity, characteristics, and associations of pain in AD patients, Silverberg et al.²⁶ performed a cross-sectional, Internet survey-based study of 602 adults in the US population. The results showed that 61% (365/602) reported pain from AD, 33% (199/602) experienced pain at least once per week, and 5% (30/602) reported pain daily. Pain was mostly associated with scratching (27%) and fissures in the skin (27%), followed by inflamed red skin (25%) or minor burning from creams or ointments (10%). More specific pain characteristics of AD are summarized in Table 1.

The level of pain is closely correlated with the severity of AD, such that pain frequency, pain intensity, and pain score represent prompts for disease evaluation.^{25,26} Misery et al.²² used DN4 (douleur neuropathique—four questions) to illustrate that 57.5% of AD patients suffered from neuropathic pain (DN4i > 3). The intensity of pain was estimated by VAS_{mean} 5.3 ± 2.9.²¹ Among a French sample of 5000 AD patients, more than half declared skin pain, and the intensity was reported to be approximately 6–10.²⁷ Recently, a novel Numeric Rating Scale (NRS) evaluation for pain among 463 adult AD patients based on questionnaires and skin examination was confirmed to be valid for clinical practice.²⁸ Although ceiling effects existed, this study would help reflect the severity of the disease. Additionally, with the distinct longitudinal course of AD skin pain, AD patients suffer long-term skin pain even when under treatment. Furthermore, the baseline level of pain appeared to predict the toughness of skin pain.²⁹

4 | BURDENS OF SKIN PAIN

Skin pain is significantly associated with impaired quality of life (QOL) using tools, such as the Dermatology Life Quality Index. Patients who had both severe itch and severe pain were likely to obtain higher scores on these measurements than patients with either of these features.^{30,31} A recent study also noted skin pain in 3834 AD patients, which interestingly reported correlated increased levels of joint pain.³²

Subjective symptoms accompanying AD can negatively influence patients' well-being, such as impaired social life, economic burden, and sleep disturbance. The coexistence of insomnia was 82% in AD patients. Sleep disturbance also crucially affects both adults and children, especially those with severe AD in adults together with early onset and persistent AD in children.^{33,34} Newer cross-sectional data involving 2893 adults with AD showed that 79.7% of the group had difficulties sleeping during the past 3 days, and sleep disturbance strongly impacted QOL, mental health, and other outcomes.³⁵ Although itch contributes a more substantial association with insomnia and sleep quality, pain is not a trivial contributor to these burdens.²¹

Skin pain may increase mental health burdens. Clinical observations have shown that patients with chronic pain exhibit symptoms of increased anxiety, depression, and cognitive impairment.³⁶ The reason is that pain is a stressor that increases autonomic sympathetic

activity and perceived stress.³⁷ Conversely, anxiety and stress have been implicated in pain hyperalgesia,³⁸ where the coexistence of pain and mood disorders may form a vicious cycle leading to a worsening disease prognosis and QOL.

Clinicians must further understand the unique burden of pain in AD patients to best evaluate clinical severity and QOL interference. Skin pain should also be regularly assessed and could be monitored as a treatment response.

5 | SYMPTOMATIC RELATIONSHIP BETWEEN PAIN AND ITCH

Studies have suggested that pain is related to scratching, fissures, and/or inflamed red skin, which is mostly because of itch.³⁹ Scratching instantly relieves the itch sensation through the activation of pain-sensory fibers that can inhibit itch sensation. This explains why people are prone to scratch if they feel itchy, and an itch-scratch cycle develops.⁴⁰ Furthermore, stimulation of thin cutaneous nerve fibers can induce an analgesic effect,⁴¹ implying that scratching may also reduce pain at the same time. Scratching is like adding insult to injury, exacerbating the already dysfunctional skin barrier. Subsequently, more pain and itch sensations are produced. What is still unknown is whether the pain originates from AD (the disease itself), or simply ensues from itch, or both.⁴²

Vakharia et al.²³ reported that 16.8% of painful AD patients thought that the skin pain was part of their itch, while 11.2% thought the pain was a result of scratching, and 72.0% thought both. Patients with skin pain were more likely to describe their itch using terms that resembled neuropathic pain. Moreover, skin pain was positively associated with AD severity and itch; the close observed relationship between itch and pain highlights the potential benefits of ameliorating skin pain in AD treatment.²⁵

6 | MECHANISM OF PAIN IN AD

Itch and pain are closely related, sharing similar pathological conditions but manifesting distinct sensations. However, pain processing in the skin is still not clearly understood in terms of the mechanism. Schmelz⁴³ summarized that three abnormal processes would result in pain and itch processing in AD, namely, decreased protective factors resulting in destruction of the skin barrier, increased levels of excitatory skin mediators and peripheral neuron sensitization, the last two of which cause activation of peripheral neurons in AD.

6.1 | Atopic skin and scratching

Sensitive skin is defined as “unpleasant sensations occurrence in response to stimuli that normally should not provoke such sensations.”⁴⁴ Dry skin and atopic predisposition may correlate with sensitive skin.⁴⁵ Research has suggested an association between

TABLE 1 The review of pain characteristics in AD from relevant references

References	Patient characteristics	AD patients affected by skin pain (%)	Skin pain severity	Driver of skin pain	Characteristics of pain	Associated topical morphologic characteristics	Other burdens
Vakharia et al. ²³	305 patients (age: 13–97 years)	42.7	Severe or very severe pain (13.8%)	Itch (16.8%); scratch (11.2%); both (72%)	Throbbing, biting, stinging, burning, sharp, tingling, pinprick-like, and crawling	Excoriations	Poor QOL, sleep disturbance, and mental health symptoms
Maarouf et al. ¹⁸	103 patients (age: 5–74 years)	78	–	Itch (61%); scratch with wound (51%); scratch without wound (60%)	Burning (73%), stinging (57%), soreness (42%), tightness (42%), tenderness (39%), and throbbing (32%)	Red (88%); cracked (73%); dry (72%); scaling (57%); crusting/scabbing (56%); swollen (54%); bleeding (51%); warm (51%); weeping/oozing (42%);	Sleep interference (80%) and leisure activity impairment (78%)
Silverberg et al. ²⁶	602 patients (age: 52.0 ± 16.3 years)	61	Moderate or severe pain (3.7%)	Scratch (27%), fissure (27%), inflamed red skin (25%), and burning from ointments (10%)	–	–	Increased self-consciousness; negative impacts on shopping, playing sports, working, or studying; and treatment burden

Abbreviation: AD, atopic dermatitis.

sensitive skin and an impaired skin barrier, with up to 80% of AD patients declaring sensitive skin.^{46,47} This finding indicates weakened integrity and stability of the epidermal skin barrier in AD patients, followed by failure of nerve ending protection, and environmental agent penetration develops sensitive skin.⁴⁶ Therefore, AD individuals are more likely to feel pain and burning sensations even though the stimuli are not strong under common conditions. Furthermore, scratching enhances itch sensations, producing an “itch-scratch-itch” cycle.⁴⁸ It is difficult to distinguish chronic pain and itch, suggesting common interacting mechanisms in between.

6.2 | Neurogenic inflammation

Peripheral mediators, especially inflammatory mediators, contribute to pain. Lysophosphatidic acid, cathepsin S (CatS), and IL-33, noted as inflammatory mediators, have implicit relationships with chronic pain conditions.⁴³ CatS activates CD4+ T cells, resulting in neuropathic pain.⁴⁹ In particular, IL-33 has been demonstrated to boost inflammation and pain in some diseases.⁵⁰ These inflammatory mediators are reported to be overexpressed in AD.^{51,52} Therefore, these results suggest that a high level of inflammatory mediators in AD activates peripheral neuron pathways.

In addition, as summarized by Liu and Ji,⁵³ compared with itch processing, cytokines including IL-1 β and IL-6 together with chemokines, such as chemokine C-C motif ligand 2 (CCL2), CCL5, and C-X-C motif chemokine (CXCL1) could induce pain.

Nerve growth factor (NGF) serves as a key substance in chronic pain conditions by primary pain afferents.⁴⁸ The level of NGF was confirmed to be increased in AD patients.⁵⁴ Evidence has also revealed the clinical relief of pain symptom by anti-NGF studies.⁵⁵

6.3 | Peripheral sensitization to pain

Inflammatory mediators activate nociceptive neurons in the pain signaling pathway. Considering peripheral sensitization to pain, G protein-coupled receptors (GPCRs) and transient receptor potential (TRP) channels, both remarkable receptor families, contribute to skin sensation.⁵⁶ Via peripheral sensitization, these receptors become activated and can transmit pain stimuli signals for further pathways.

TRP vanilloid 1 (TRPV1), TRP ankyrin 1 (TRPA1), and transient receptor melastatin member 8 (TRPM8) are TRP channels that are detected at high levels in AD lesions.^{57,58} Activation of TRPV1 results in increased levels of proinflammatory neuropeptide substance P, accelerating neurogenic inflammation.⁵⁷ Mas-related GPCRs (Mrgprs), serving as members of the GPCR superfamily, are expressed by primary sensory neurons for peripheral skin sensations.^{59,60} Mas-related GPCR D (MrgprD) is likely to be involved in neuropathic pain mechanisms as a nociceptor and mediate pain signaling.^{61,62} Moreover, β -alanine-responsive QC fibers activate MrgprD expression, resulting in capsaicin pain.⁶³

Nociceptors become stimulated by mass fibers and signal the process of pain and itch. Pain neurons and touch neurons can sense skin stimuli and conduct pain until the brain. However, these receptors can also inhibit the signaling pathways of itch by GABAergic interneurons and glycine interneurons.⁴³

6.4 | Central sensitization to pain

The endothelin-1/endothelin receptor type B (ET-1/EDNRB) pathway was implicated in an atopic mouse model to explain the correlation between neuropathic pain and allergic inflammation, as also supported by an enhanced level of ET-1 in atopic patients.⁶⁴ This study implied that ET-1/EDNRB mediates spinal astroglia and microglial activation in AD, inducing neuropathic pain.⁶⁴ Conclusively, peripheral sensation and activation of the nervous system would transmit the pain signal. The activation of spinal microglia boosts the expression of cytokines including IL-1 β and TNF- α and brain-derived neurotrophic factor.^{53,65} Moreover, the activation of astroglia results in the increased release of CCL2.⁶⁶ Consequently, these mediators regulate pain processing and central sensitization.

In addition to the evidence above, chronic pain-associated brain areas are activated in the anterior cingulate cortex, insula, and dorsolateral prefrontal cortex of the brain in AD patients, as observed by brain imaging.⁶⁷

6.5 | Pain and itch

Itch and pain share largely overlapping mediators and receptors such as TRPV1, TRPA1, TLRs, and PARs, both in physiological and pathological conditions. Itch stimuli can be perceived as pain in some chronic neuropathic pain conditions.⁶⁸ While differences between acute pain and acute itch are striking, chronic pain and chronic itch share many similar mechanisms, including peripheral sensitization, central sensitization, loss of inhibitory control in the spinal cord, and neuroimmune interactions at peripheral and central levels.⁶⁹

On the one hand, pain inhibits itch. Some studies of hydrogen peroxide showed that pruritogens at higher doses in rodents produce pain to suppress itch.⁵³ Another study showed that glutamate released from the central branches of nociceptors not only triggers pain transmission but also activates inhibitory neurons for itch suppression.⁷⁰ Research on the skin of the normal population has shown that itch can be significantly reduced by applying conditioning pain.⁷¹ These findings parallel the condition that after scratching (regarded as a kind of pain stimulus), itch is reduced to some extent. For the opposing role of pain suppressing itch, inhibition of pain may produce itch in turn.⁷² This possibility is partly supported by the process by which pain-inhibiting opioids generate itch.⁷³

On the other hand, however, under pathological conditions, such as AD, painful stimuli may not be sufficient to suppress itch, whereas they may instead enhance itch in these chronic itch patients.⁴² Some painful stimuli may evoke itch in patients with dermatitis but not in

normal people. Taking bradykinin as an example, which evoked only weak pain in nonlesional or normal skin, it was observed to induce intense itch in lesional skin, indicating that simultaneous pain stimuli increase itch conversely.⁷⁴ Existing studies found that cutaneous innervation is reduced in pruritic skin, as itch receptors are unregulated to drive ongoing itch.⁷⁵ This hypersensitization may lead us to wonder whether pain sensation is upregulated simultaneously.

As comprehensively theorized based on clinical observations, pain and itch processes are differentiated by spatial and temporal patterns, originally caused by neuropathy and inflammation, as mentioned before.⁴³ It remains controversial whether pain-killing treatment would aggravate itch, although it is widely accepted that some drugs for treating chronic pain are also effective in chronic itch because of the interlinking mechanism. Rather than separating itch and pain, research concepts should address the overlapping mechanisms as chronic inflammatory conditions.

7 | MANAGEMENT OF PAIN IN AD

The overwhelming majority of AD therapies have been proven effective in treating annoying itch; however, pain is always poorly studied and understood. Skin pain may be useful as a marker of treatment progress and disease severity since it introduces indispensable burdens. Nonetheless, the relationships of skin pain with disease severity, anatomical location, and the use of pain medication are still unclear and require further investigation.

To examine analgesic medication in AD patients, Thyssen et al.²⁵ performed a cross-sectional study of 3208 randomly selected adults from the general population and 3834 adults with a diagnosis of AD in Denmark. Skin pain was positively associated with AD severity and itch, while pain medication (including paracetamol, nonsteroidal anti-inflammatory drugs, and opioids) was not significantly increased. Other drugs, such as gabapentin⁷⁶ and pregabalin⁷⁷ have been used in patients with severe AD.²⁵ In addition to paracetamol, tramadol, or other analgesic, there are some other treatments for alleviating pain, for example, treatments, such as vagus nerve stimulation⁷⁸ and acupuncture,⁷⁹ but clinical application of these treatments in AD patients has not yet been reported. Nevertheless, analgesic and gabapentinoid treatment requires a comprehensive evaluation of patient age, medical history, pain intensity, and drug effects.⁸⁰

The principal therapy to manage pain and itch is topical therapy.⁸⁰ The use of emollients is considered to prevent lesions from becoming painful.⁸¹ There is still a lack of evidence to confirm pain relief by many AD treatments. Moreover, some topical treatments for AD may even evoke pain sensation. When the lesion is worsened by infections, which would promote pain processing, specialized antimicrobials and antiseptics are recommended for treatment.⁸²

Topical therapies for AD include topical corticosteroids (TCSs), calcineurin inhibitors (TCIs), and new topical treatments, such as topical phosphodiesterase 4 (PDE4) inhibitors, novel topical Janus

kinase (JAK) inhibitors, tofacitinib and delgocitinib, and UV therapy. Systemic treatments have provided limited evidence regarding pain relief of patients.⁸⁰ Most of the treatments present great effects in reducing itch; however, few papers have reported diminishment of pain in AD patients. It is still unknown whether TCSs reduce pain.

Calcineurin inhibitors are related to a reduction in pain hypersensitivity.⁸⁰ For example, FK506 (tacrolimus) is an immunosuppressant widely used as an ointment in the treatment of AD. Local application of FK506 might evoke burning sensations, and some patients have felt pain after using FK506 topically. The underlying mechanism might be explained by FK506 mediating TRPA1 activation.⁸³ To lower the side effects of FK506, a microemulsion system integrating FK506 into a menthol/camphor eutectic might be helpful, owing to their cooling nature in topical analgesics.⁸⁴

However, recent studies have provided new perspectives on biological treatments related to pain induction. JAK inhibitors have been shown to palliate pain. Baricitinib, a JAK inhibitor, was reported to reduce patient-reported pain in AD patients, with a remarkable decrease in NRS responders, and to further enhance their QOL.⁸⁵ Additionally, significant amelioration of pain symptom in moderate-to-severe AD was observed after dupilumab (IL-4R α mAb) treatment.⁸⁶

One problem is that doctors fail to ask AD patients about skin pain symptom, which has aroused public attention, as 79.4% of AD patients did not receive help from physicians due to a lack of solicitude.¹⁷ As advocated by Fuxench,⁴ the assessment of pain represents a research hotspot needing better understanding.

Therefore, to address the complaint of pain among AD patients, the primary treatment is to apply AD therapy supplemented with emollients, general principles and education, and psychological assistance. If pain persistently exists, several therapies can aid the situation, including analgesics, gabapentinoids, antidepressants, anti-JAK, anti-PDE4, and μ -opioids.⁸⁰

In summary, the higher prevalence of pain in AD than previously thought and the close but not fully determined relationship between itch and pain highlight the potential benefit of establishing more sound treatments to ameliorate itch and relieve skin pain.

8 | CONCLUSIONS

Skin pain in AD has been characterized as an increasingly remarkable symptom. Clinicians and health policy experts should be aware of the related characteristics between pain and itch. Future research is needed to clarify the commonality and disparity of these two apparent symptoms in order to seek efficacious medications.

ACKNOWLEDGMENTS

All authors permit the submission of the study. This study was supported by the National Natural Science Foundation of China (81602765; Dr. Yueping Zeng). We declare that the article has not been submitted to another journal, and it has not been published in whole or in part elsewhere previously. We thank Mr. Xiao-Yong Fu

from the Wharton School of the University of Pennsylvania for his kind help in revision of language. We also thank Springer Nature Author Service (SNAS) for their kind help in language editing and overall style of the manuscript.

CONFLICT OF INTEREST

We declare that we have no conflicts of interest.

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How to cite this article: Li J-X, Dong R-J, Zeng Y-P.

Characteristics, mechanism, and management of pain in atopic dermatitis: A literature review. *Clin Transl Allergy.* 2021; e12079. <https://doi.org/10.1002/ctt2.12079>