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INVITED ARTICLE

Chronic pruritus – pathogenesis, clinical aspects and treatment

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Abstract

Chronic pruritus is a major symptom in numerous dermatological and systemic diseases. Similar to chronic pain, chronic pruritus can have a dramatic impact on the quality of life and can worsen the general condition of the patient considerably. The pathogenesis of itch is diverse and involves a complex network of cutaneous and neuronal cells. In recent years, more and more itch-specific mediators and receptors, such as interleukin-31, gastrin-releasing peptide receptor or histamine H4 receptor have been identified and the concept of itch-specific neurons has been further characterized. Understanding of the basic principles is important for development of target-specific treatment of patients with chronic pruritus. In this review, we summarize the current knowledge about the pathophysiological principles of itch and provide an overview about current and future treatment options.
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Keywords

atopic dermatitis, itch, mast cell, pruritus, urticaria

Key points

- Chronic pruritus is a common problem affecting a large proportion of the population.
- The pathophysiological mechanisms underlying chronic pruritus are still insufficiently understood.
- In the skin, diverse and complex interactions of keratinocytes, mast cells and sensory nerves largely determine the occurrence and the control of pruritus.
- Management of patients with chronic pruritus requires an individually tailored therapy based on the condition of the skin (inflamed or non-inflamed), possible underlying causes and existing co-medication.
- Systemic treatment with antihistamines often requires up-dosing up to 4-fold of the recommended daily dose.
- Alternative systemic treatments of chronic pruritus are anticonvulsant drugs, μ-opioid receptor antagonists, antidepressants and UV light therapy.
- Novel treatment options for chronic pruritus are to be expected in the near future and include H4 receptor antagonists, κ-opioid receptor agonists and neurokinin 1-receptor antagonists.

Conflict of interest

M Metz was or is speaker for Abdi Ibrahim, Essex Pharma, Merckle-Recordati, MSD, Novartis Pharma, Uriach Pharma. S Ständer was or is consultant, speaker and/or investigator for Aesca Pharma, Almirall/Hermal, Astellas Pharma, Beiersdorf AG, Birken, Essex Pharma, Pierre Fabre, Maruho, 3M Medica, Mundipharma, Novartis Pharma, Serentis, Serono and Stiefel Laboratorium.

Introduction

Itch (syn.: pruritus) is a very common symptom that almost everyone has experienced in his or her lifetime, for example after an insect bite or after contact with a stinging nettle. In these cases, itch may be annoying and bothersome, and the centuries old definition of pruritus as an unpleasant sensation that triggers a desire to scratch [1] is still the most apt description for it. As an acute sensation, pruritus fulfils an essential part of the innate defence mechanism of the body. Next to pain, itch serves as an alarm system to remove possibly damaging or harming substances from the skin. If itch persists for 6 weeks or longer, it is defined as chronic pruritus by the International Forum for the Study of Itch (IFSI).[2] Chronic pruritus is a major diagnostic and therapeutic problem and can have a profound impact on the patients' quality

of life. It can occur in patients suffering from numerous different diseases, for example inflammatory skin diseases, metabolic disorders, liver and kidney diseases, or lymphoproliferative and myeloproliferative disorders. The underlying causes and the mechanisms of itch are diverse and only partly understood. A better understanding of the pathophysiology and also about the prevalence, incidence, and the socio-economic impact of pruritus is needed to improve the diagnosis and treatment of patients with chronic pruritus.

Epidemiology of chronic pruritus

Epidemiological data on chronic pruritus are still scarce, and published frequencies of chronic itch as a symptom in different diseases often vary strikingly within the same disease. In recent years, however, more investigations have been carried out to characterize chronic itch better in the general population as well as in patients with specific diseases. In a recent report, Weisshaar and Dalgard provide thorough information on these findings, and readers are referred to this review for in-depth information.[3]

The prevalence of chronic itch in the general population has been reported to range from 8.4% in a large cross-sectional study with more than 40 000 adults in Norway[4] to 13.9% in a smaller German pilot study with 200 adults.[5] Frequency of pruritus as a symptom of specific dermatological diseases can be found more often in the literature. For example, in various studies of patients with psoriasis, itch was reported in up to 87% of the patients, whereas patients with atopic dermatitis and urticaria suffer 100% from pruritus.[3] In internal diseases, itch is best studied in uraemic diseases where the prevalence is reported to range between 10% and 70% and hepatic diseases where chronic itch was described in 15–100% of the cases.[3]

Classification of itch

Chronic pruritus can be classified based on aetiological or symptom-associated criteria[2,6] (Table 1).

Based on the aetiology of pruritus in the skin, its transmission and modulation in the central nervous system (CNS), pruritus is classified in four different categories:[6] (i) Pruriceptive pruritus, which is transmitted through C-fibres and originates directly in the skin, for example as a consequence of skin diseases such as psoriasis or dry skin. (ii) Neuropathic pruritus, caused by damage of the itch-transmitting afferents of the peripheral nerves or the spinal cord, e.g. in brachioradial pruritus, postherpetic pruritus or notalgia paraesthetica. (iii) Neurogenic pruritus, which occurs because of diseases of central structures of the CNS such as brain tumours or abscesses. (iv) Psychogenic pruritus (e.g. tactile hallucinations, delusional parasitosis), which is mostly based on metabolic disorders in the CNS.

The clinical symptom-associated classification of pruritus takes into account that it can be difficult to identify the underlying cause of pruritus from the clinical picture. Therefore, pruritus is first classified by the clinical picture and then as a second step categorized in the respective diseases, if needed after further histological, laboratory and radiological investigations[2] (Table 1).

Table 1 Classifications of chronic pruritus

Neuroanatomical classification
Based on possible origin of pruritus
• pruritoceptive: pruritus arising in the skin
• neuropathic: pruritus resulting from peripheral nerve damage
• neurogenic: mediators produce pruritus in the CNS without nerve damage
• psychogenic
Clinical classification
Step I. Based on clinical picture
• Pruritus of primarily inflamed skin
• Pruritus of primarily non-inflamed skin
• Pruritus with chronic secondary scratch lesions (prurigo)
Step II. Based on potential underlying disease
• dermatologic diseases
• systemic diseases
• neurological diseases
• psychosomatic/psychogenic diseases
• mixed
• other (unknown cause)

Pruritus on primarily non-inflamed skin is defined as generalized or localized pruritus without initial occurrence of skin changes. For example, pruritus in cholestatic liver diseases induces itch without obviously affecting the skin. In former times, the term *Pruritus sine materia* was often used to describe itch on primarily non-inflamed skin.

Pruritus on primarily inflamed skin is defined by itch occurring in association with an inflammatory skin disease (atopic dermatitis, urticaria, psoriasis, cutaneous lymphoma, etc.). Scratch lesions such as linear or round erosions, excoriations, crusts to lichen simplex, lichen amyloidosus or prurigo nodularis have to be seen separately. These conditions that previously have been described as independent entities are seen today as a secondary scratch-induced phenomenon, preceded by pruritus based on primarily inflamed or non-inflamed skin.

Pathophysiology of itch in the skin

In the skin, many factors contribute to the induction, exacerbation or suppression of pruritus. For example, physical stimuli such as cold and heat modulate the perception of itch; painful heat and cold can significantly diminish it, whereas moderate cold intensifies it.[7] Mechanical factors such as rubbing or scratching the skin can briefly suppress itch by activating nerve fibres that selectively activate and de-activate certain areas of the brain.[8] The most important factors in the elicitation of itch are, however, resident skin cells that can release mediators that directly induce itch by binding to pruriceptors or indirectly by releasing products that activate other cells to release pruritogenic substances (Fig. 1).

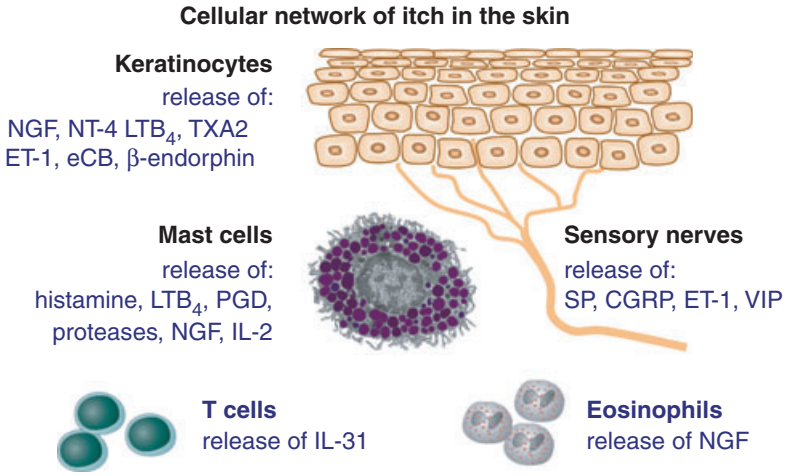

Figure 1 Itch-associated cells and mediators in the skin. Induction, perception, maintenance and control of pruritus involve a complex network of various cells and mediators. Here, some of the cells and mediators are listed. NGF, nerve growth factor; NT-4, neurotrophin 4; LTB_4, leukotriene B4, TXA2, thromboxane A2; ET-1, endothelin-1; eCB, endogenous cannibinoids; PGD, prostaglandine; IL-2, interleukin-2; SP, substance P; CGRP, calcitonin gene related peptide; VIP, vasoactive intestinal peptide.

Keratinocytes

One of the essential functions of epidermal keratinocytes (KC) is to provide an effective barrier against physical, chemical and biological environmental factors. Epidermal KC are specialized in many ways to exert their crucial role as outpost of the innate defence system. Induction of itch in the skin is an important defence mechanism to detect and instantly remove possibly harmful substances from the skin by scratching. Therefore, the epidermis has to provide ways for detection of potential threats and for transmitting itch via the production and release of pruritogenic mediators and has to be in close contact with sensory nerves. Disruption of this system therefore often promotes or even induces chronic pruritus.

Keratinocytes can be activated to produce and release inflammatory and pruritogenic substances by various innate mechanisms, e.g. toll-like receptors (TLR), UV light or thermoreceptors.[9,10] Furthermore, KC can detect other itch-associated signals, for example by expression of protease-activated receptor-2,[11] opioid-,[12] cannabinoid-[13] and histamine H4 receptors.[14] By responding to these signals, KC can modulate itch in many ways. For example, keratinocytes can release neurotrophins such as nerve growth factor and neurotrophin-4,[15,16] lipid mediators[17] or endothelin-1[18] (Fig. 1) that can either directly activate itch fibres in the skin or activate mast cells to release pruritogenic mediators. KC may also be involved in down-modulation of pruritus, for example through the release of endocannabinoids, which can directly bind to inhibitory receptors on sensory nerves.[13]

Mast cells

Mast cells (MC) are located in close vicinity to epidermal and hair follicle keratinocytes, blood vessels and sensory nerves, and they express a large number of receptors that can activate the cells to release its mediators.[19,20] As many of these mediators are known to be involved in the elicitation of itch, MC have a central role in the cellular network of pruritus.

Of all mediators that are known to induce pruritus, MC-derived histamine is the best known and most thoroughly researched. Preformed histamine is present in large amounts in mast cell granules and thus, after cell activation, it can be immediately released into the surrounding area where it can induce pruritus via H1 receptors on nerve fibres. Apart from H1 receptors, histamine modulates pruritus also by H3 and H4 receptors. While the pharmacological blockade of H4 receptors has been shown to reduce pruritus significantly in mouse models,[14,21] H3 receptors appear to be involved in the suppression of pruritus as H3 receptor antagonists have been shown to induce pruritus in mice.[22] Although it is known from experimental studies and from certain skin disorders such as urticaria that histamine can lead to intense pruritus, in clinical practice, pure histamine-induced itch is rare. This is also reflected in the excellent antipruritic effect of antihistamines in urticaria and their limited effect in other itch-associated disorders.

Apart from histamine, many other MC-derived substances have been identified to be involved in the induction or modulation of itch. For most of these substances, the clinical relevance remains, however, to be determined. Among the pruritogenic mediators are for example proteases, lipid mediators, neuropeptides and various cytokines. Other substances that are not produced by MC have been shown to induce or exacerbate pruritus without directly affecting nerve fibres through indirect effects as a result of mast cell activation in the skin. Although these are broadly referred to as histamine liberators, the activation of MC may also lead to the

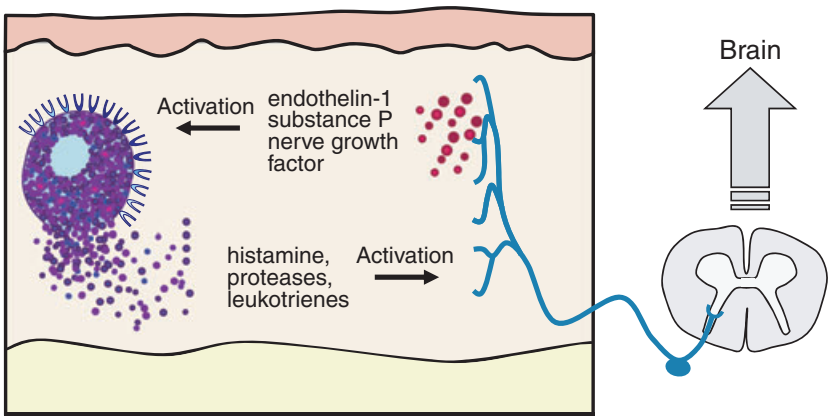

Figure 2 Nerve-mast cell interactions. Mast cells and nerves can interact in many ways, depicted here are examples of possible interactions in pruritus.

release of other pruritus-inducing substances. Among the most relevant MC activators in pruritic diseases are neuropeptides such as vasoactive intestinal peptide (VIP), calcitonin gene related peptide (CGRP), substance P and endothelin-1 (Fig. 2). In a mouse model, it has been shown for example that a MC-mediated allergic reaction is markedly diminished in the absence of sensory cutaneous nerves.[23]

Other cells

The induction, exacerbation or suppression of pruritus in the skin appears to be orchestrated by a complex interplay of many factors and may differ depending on the pathophysiological changes in the skin. In inflammatory skin diseases, infiltrating cells can be, at least in part, responsible for the induction or exacerbation of pruritus. Atopic dermatitis (AD) for example is characterized by a dermal and epidermal infiltrate of eosinophils that can contribute to the enhanced levels of nerve growth factor (NGF) measured in the skin of AD patients[24,25] and thus to the persistence of pruritus in these patients. Furthermore, T-cell-derived interleukin-31 (IL-31) has recently been shown to induce severe pruritus in mouse models of AD and to be highly up-regulated in the skin of AD patients.[26,27] Furthermore, IL-31 antibodies have been shown to reduce itch significantly in a mouse model of AD.[28]

Pathophysiology of itch in the nervous system

In the skin, pruritus is mediated by free nerve endings of non-myelinated nerve fibres that are located at the dermoepidermal junction and within the epidermis. For a number of diseases that involve itch, such as atopic dermatitis, prurigo nodularis and allergic contact dermatitis, it has been suggested that the increased production and release of NGF from resident skin cells such as KC or MC lead to an increase in 'itch fibres' in the skin possibly leading to exacerbating pruritus.[1]

After the induction of itch in the skin, specialized nerve fibres are responsible for the transmission of the sensation to the central nervous system. For example, subpopulations of pruritus-specific non-myelinated C nerve fibres exist that respond only to histamine and there is evidence of other specific, histamine-independent itch fibres in the skin.[29] Very recently, specific G protein-coupled receptors that mediate chloroquine-induced pruritus have been identified in murine peripheral sensory neurons.[30] These neurons also respond to other itch inducing signals such as histamine and capsaicin, and express gastrin-releasing peptide receptor that has previously been shown to be importantly involved in the transmission of itch, indicating that the receptor expressing neurons may be itch-specific.[31] It has very recently been suggested that another key element of the spinal transmission of itch includes neurokinin-1 expressing dorsal horn neurons that indicates that substance P may play a role as a spinal neuropeptide transmitter for itch.[32] Accordingly, neurokinin-1 receptor antagonists showed significant relief of pruritus in a proof-of-concept study.[33]

Pruritus can arise peripherally and then be transmitted to the central nervous system, or it can originate in the CNS or spinal cord. Intrathecal administration of VIP, CGRP, and substance P, or opioids has been shown in various animal studies to cause reactions such as scratching, biting, and other pruritus-related reactions.[34] In human studies, there are also reports of onset or worsening or pruritus after perioperative intrathecal or intraspinal administration of opioids.[35] The origin of pruritus in such cases has not been fully elucidated, although studies on monkeys have clearly shown that a central activation of μ-opioid receptors is responsible.[36]

In the central nervous system and spinal cord, pruritus can also be suppressed or obscured by pain stimuli. The gate-control theory suggests that pruritus is suppressed by mechanical or electrical stimulation of rapid-transmitting myelinated A fibres at the spinal level in favour of transmitting pain sensation. This mechanism

would explain, for instance, the antipruritic effect of the pain induced by scratching.

Peripheral and central sensitization to itch

The reasons for a persistence of itch and thus for chronic pruritus may be manifold; the peripheral and central nervous systems, however, seem to play an important part. As described above, there are a number of inflammatory mediators that can lead to activation of pruritus-mediating nerve fibres. In addition to this direct effect, some of these substances can also produce longer-term changes in the skin. Some patients with atopic dermatitis demonstrate significantly elevated levels of NGF and substance P (SP),[37] which can contribute to an increase in cutaneous itch fibres and thus to more intense and possibly chronic pruritus.[38] In addition, by inhibiting apoptosis and inducing the proliferation, NGF also leads to an increase in mast cells[16] and to up-regulation of other potentially pruritogenic substances such as SP,[1] both of which worsen existing pruritus or cause it to persist. Chronic stimulation of neuroreceptors such as histamine or capsaicin receptor (TRPV1) by inflammatory mediators such as bradykinin, prostaglandins and neurotrophins ultimately leads to a reduction in the stimulus threshold of these receptors. These mechanisms are understood as peripheral sensitization that leads to sensitized nerve fibres that more readily trigger pruritus.[38,39]

Central sensitization to pruritus has already been described by numerous authors. Similar to pain sensitization, alloknesis as well as hyperknesis can occur in pruritus, i.e. itch triggered by normally non-pruritogenic stimulus, worsening of pruritus by a stimulus that normally would not cause itch, or a normal itch stimuli that is perceived as an intense sensation.[40] Studies on patients with atopic dermatitis have shown that normally painful stimuli such as electrical stimuli or application of acetylcholine to skin lesions may be perceived as itch.[41] In patients with pruritus associated with inflammatory skin changes, this means that numerous physical, chemical, or biological stimuli can sustain or exacerbate existing pruritus.

Clinical aspects

Many different dermatological and non-dermatological diseases are associated with sometimes intense chronic pruritus, but the clinical picture is usually characterized by the characteristic features of the underlying disease (Fig. 3). Only some patients can readily be identified to suffer from pruritus by presenting with secondary skin changes due to scratching. These cutaneous lesions can include erosions, excoriations, crusts, necrotic areas, but also lichenification, nodules, hyper- or hypopigmenation, and scarring. Typically, patients with chronic pruritus report various qualities associated with itch. These include pure itch, itch after mechanical stimuli, aquagenic pruritus, or mixed symptoms with pruritus, pain, burning, or stinging. Some diseases may have so called clinical sensory characteristics (Table 2), and together with time of onset and localization of pruritus, these sensory patterns may help to diagnose the underlying cause of pruritus.[42]

Therapy of pruritus

General aspects

The current guidelines for the treatment of pruritus in Germany recommend a step-by-step treatment procedure, tailored to the severity of symptoms, accompanying diseases, patient age, comedications, and the severity of lesions due to scratching.[43] In general, several treatment modalities are selected, given that not only pruritus but also secondary scratch lesions require treatment. Many patients require combination of systemic and topical therapies. If approved medications fail to achieve a reduction in pruritus, alternative therapies may be chosen that have demonstrated an antipruritic effect in studies, followed by therapies for which there are case series, case studies and expert opinions available.

Elimination of triggering factors

External factors affecting the skin can intensify pruritus or trigger more itch. These include physical factors such as overheated rooms, insulating clothing, or being in a warm bed. Also, factors that irritate the surface of the skin, such as rough fabrics or wool clothing should be avoided. An important factor in itch is dry skin, which may be exacerbated by frequent washing or use of soap. Before doing anything else, a moisturizing therapy should be initiated as a basic therapy. Another important issue is the treatment of lesions caused by scratching. Classic dermatological therapies (e.g. emollients, topical corticosteroids, short-term relief with polidocanol, urea, menthol) have proven effective. Internal factors can also intensify the perception of itch. These include hot spices, alcohol, hot beverages, a wide array of medications (e.g. β-blockers, allopurinol) and psychogenic factors such as tension and stress.

Topical antipruritic therapies

Adult patients with local, severe pruritus, chronic local lesions from scratching (e.g. lichen simplex, prurigo nodularis), psoriasis, or pain such as postherpetic neuralgias, may be treated with capsaicin cream.[44] Erosions should be treated before beginning of therapy, as contact with skin lesions can cause severe burning. Use in paediatric patients is limited given the initial burning sensation that can be extremely intense if there is contact with mucous membranes.

In addition to their anti-inflammatory effect, there are numerous reports of an antipruritic effect of the calcineurin inhibitors tacrolimus and pimecrolimus. In atopic dermatitis, for instance, pruritus has reportedly resolved within a short time. Other diseases that involve itch also respond to pimecrolimus and tacrolimus. For instance, patients with prurigo, chronic irritant hand eczema and genital pruritus have also been successfully treated with calcineurin inhibitors.[45]

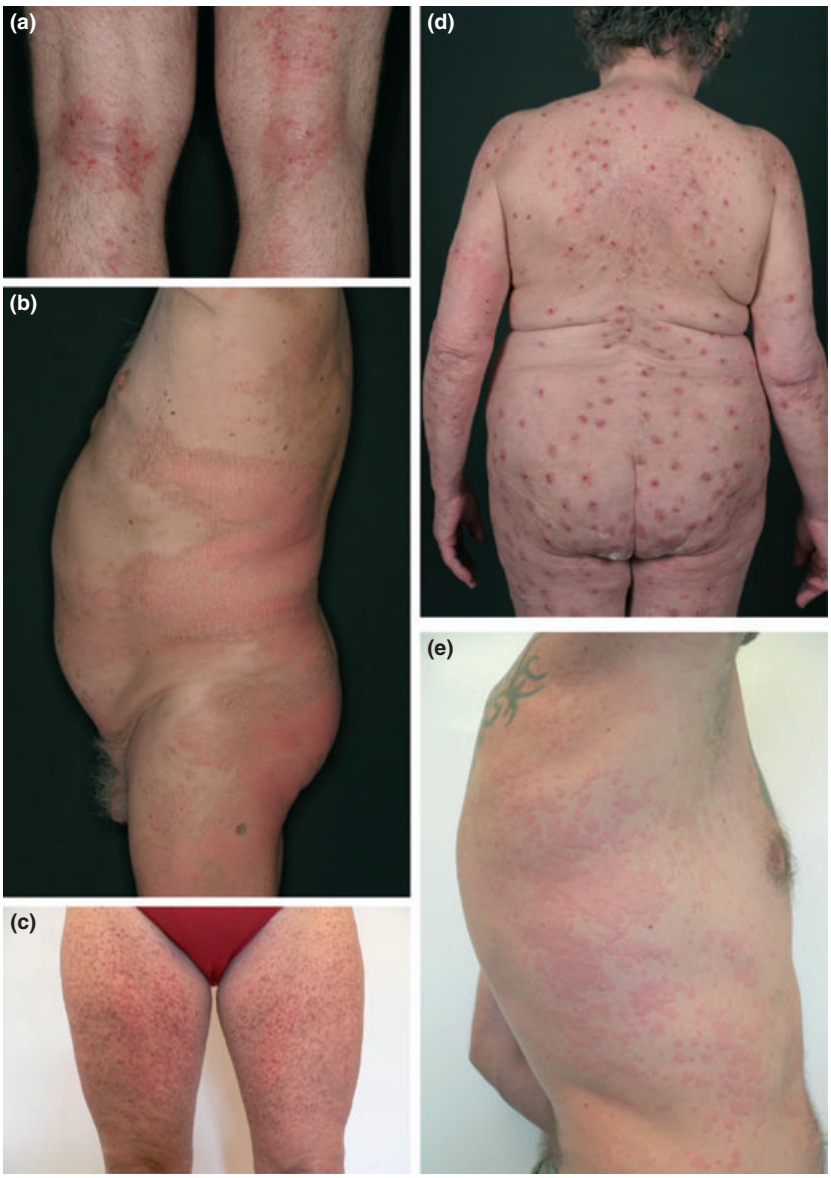

Figure 3 Patients with severe chronic pruritus. (a) atopic dermatitis, (b) mycosis fungoides, (c) cutaneous mastocytosis, (d) prurigo nodularis, (e) chronic spontaneous urticaria.

In the past few years, there have been reports on the use of topical cannabinoid agonists for treatment of pruritus in experimentally induced pruritus[46] as well as in patients with atopic dermatitis.[47]

Systemic therapies

Modern systemic treatments for pruritus include not only known dermatological therapies. Many substances that are effective in the central nervous system have also been analysed with regard to their antipruritic potential and often used to treat pruritus. The following presents a selection of the most common therapies and information on their proven or hypothesized mode of action in the suppression of pruritus.

Antihistamines

H1-Antihistamines are a popular treatment option in chronic pruritus because they are approved for treatment and are affordable. However, similar to chronic urticaria where the current recommendation is to increase the dose of antihistamines up to 4-fold if regular dosing is not effective[48], chronic pruritus also often requires the up-dosing of non-sedating antihistamines. The main antipruritic effect of H1-antihistamines is the blockade of

Table 2 Typical itch characteristics of various diseases

	Diagnosis	Patient history, affected site*	Type of itch*
Internal diseases	Kidney disease requiring dialysis	2–3 months after initiation of dialysis, generalized or localized, often additional xerosis, often prurigo	Pure itch, occasionally attacks of itch or stinging during or right after dialysis, often very severe
	Cholestatic diseases	Generalized pruritus, especially on distal extremities; typically triggered by tight clothing; few lesions from scratching	Pure itch; can be mechanically induced; not diminished by scratching, scratching is avoided
	Polycythemia vera	Generalized pruritus, prurigo possible	Stinging, aquagenic itch: pruritus after contact with water
	Hodgkin's disease	Pruritus in area of affected lymph nodes, generalized in conjunction with mediastinal sites, premonitory onset	Itch only
Drug-induced pruritus	Hydroxyethyl starch (HES)	After infusions with large cumulative doses (>200 g), no lesions from scratching!	Mechanically induced pruritus with attacks of stinging, can be triggered by rubbing, etc., scratching is avoided
	Drug-induced pruritus	Temporal relationship is often uncertain, occurs usually after several months, typical drugs: cytostatics, cytokines, statins	Itch only
Neurological disorders	Brachioradial pruritus	In the area of brachioradialis muscle (C6 dermatome), unilateral or bilateral, trigger: UV light, possible prurigo	Neuropathic pruritus: itch with painful qualities such as burning, stinging, biting, piercing, tingling
	Notalgia paraesthetica	Pruritus between the shoulder blades, or possibly other areas on the back, hyperpigmented maculae	Neuropathic pruritus
Psychiatric disorders	Somatoform and dissociative disorders, schizophrenia	Pruritus often starts on the head, possibly spreading to the upper trunk or whole body, occasionally with severe lesions resulting from scratching	Itch with painful qualities such as burning, stinging, biting, piercing, tingling
	Tactile hallucinations, delusional parasitosis	Interpretation of symptoms as moving skin parasites, particles are collected as evidence	Pruritus, stinging, tingling, sometimes moving up or down the extremities
	Adjustment disorder	Reactive depression to long-standing pruritus	Pruritus characteristics are the same, with additional depression or other psychosomatic symptoms
	Emotional factors	Anxiety, fatigue, stress, burn-out syndromes, or personality disorders exacerbate existing pruritus	Increased itch, occasionally stinging
Skin diseases	Atopic dermatitis	Pruritus with flare-ups or in the interval in between	Itch, occasionally focal stinging, burning after scratching; scratching exacerbates pruritus; allokinesis
	Psoriasis	Strictly limited to the psoriatic plaques	Itch only
	Urticaria, mastocytosis	Purely itch with oedema, erythema	Histamine-mediated pruritus, sometimes mechanically induced, scratching is avoided

*The content of the table is based on clinical observations.

H1 receptors on C-afferent fibre terminals.[49] Recently, it has been suggested that modern antihistamines may, at least in higher dosages, be able to also prevent degranulation of mast cells.[50,51] As mast cells not only release histamine but can also release other pruritogenic mediators, this may add to the antipruritic effects.

Anticonvulsant drugs

In clinical practice, anticonvulsants have often demonstrated potent analgesic effects and are approved for use in neuropathic pain of various causes (e.g. diabetic neuropathy), but they have also been shown to be effective in the treatment of pruritus. Gabapentin or pregabalin is considered to be a good second-choice therapy.[52] The exact mechanism of action for these drugs is, similar as in pain management, not yet clarified. The current concept is that they reduce the stimulated release of transmitters by binding at specific calcium channels.[53] An interesting new theory is that gapapentin and pregabalin may enhance analgesia by reducing the affective and aversive aspects of pain.[53] This could be of similar importance in the suppression of itch.

Opiate receptor antagonist or agonists

Naltrexone is the only oral opioid receptor antagonist with a long-lasting, selective blockade of μ-opiate receptors available in Europe. It has been shown in many case series and controlled trials to be partially effective in relieving pruritus mainly associated with chronic kidney diseases[54] and patients with liver diseases, but also in various dermatological diseases.[55] Activation of μ-opioid receptors reduce the activity of pain-transmitting neurons and suppress their inhibitory effects on pruriceptive neurons. Antagonists of μ-opioid receptors can therefore restore the physiological suppression of itch.[55]

Based on the assumption that opioid-induced itch is mediated by activation of μ-opioid receptors and can be suppressed by activation of κ-opioid receptors, it was thought that κ-agonists may be an effective treatment of itch. First clinical trials support this hypothesis; recently, it was shown that the κ-receptor agonist nalfurafine effectively reduced itch in treatment refractory haemodialysis patients.[56]

Antidepressants

Antidepressants have long been used in the treatment of chronic pruritus. Many antidepressants have antipruritic properties that, however, are often not reported in studies, but are merely cited by experts. The following discusses only those preparations for which study results are available. The antipruritic effectiveness of the selective serotonin reuptake inhibitors (SSRI) paroxetine and sertraline has been documented in controlled studies and case reports for various systemic disorders. Severe pruritus reportedly responded in patients with polycythaemica vera, somatoform pruritus, paraneoplastic pruritus and cholestatic pruritus.[57,58]

Mirtazapine is a tetracyclic antidepressant with additional H1 antihistaminic and serotonergic effects. It has successfully demonstrated an antipruritic effect in idiopathic pruritus, cholestasis, uraemia and neoplasm-induced pruritus.[59]

The tricyclic antidepressant doxepin is used topically and systemically for its additive antihistaminic and anticholinergic effects in pruritus. In a study on mustard gas-induced pruritus, doxepin and the sedating antihistamine hydroxyzine were about equally effective in three-fourths of patients.[60]

The exact mechanisms underlying the documented antipruritic effects of the described drugs are not entirely clear. One important aspect, especially of the tricyclic and tetracyclic antidepressants, may be the known antihistaminergic effect of these drugs. Furthermore, central nervous effects of serotonin are thought to have a regulatory action on the itch-related transmission.[57]

UV light therapy

Whole-body phototherapies with ultraviolet A or ultraviolet B (UVA or UVB) light, separately or in combination, have been shown to be effective in pruritus of different aetiologies.[61–63] UV therapy can be especially useful in patients with contraindications to systemic agents, for example during late-term pregnancy, in older patients, in those with multiple prior diseases or who are taking several medications. UV therapy can also be used in patients in whom other antipruritic therapies have failed. UV light therapy is not advised for patients who are taking topical calcineurin inhibitors. Although the exact mechanism of UV light-induced reduction of itch is not known, an intriguing hypothesis stems from data showing that in patients with chronic pruritus and atopic dermatitis the κ-opioid, but not the μ-opioid system is downregulated in the epidermis. Psoralen UVA therapy restored the normal expression of the κ-opioid system that was concomitant with a decrease in itch severity in these patients.[64]

Novel and experimental therapies

In recent years, pruritus has gained more and more attention and is appreciated as an important symptom that can dramatically reduce quality of life in patients. This new focus on itch as a specific target has lead to the development of novel drugs that are currently tested in clinically trials or which are currently under development. Among them are for example histamine H4 receptor antagonists[65] and κ-opiod agonists.[56] Furthermore, some drugs have been reported in case reports or small case series to be highly effective in suppressing pruritus. For example, the neurokinin 1-receptor antagonist aprepitant was shown to be able to control almost completely the severe and treatment refractory pruritus in three patients with Sézary syndrom[66] and 20 patients with pruritus and prurigo nodularis.[33] Randomized controlled trials have to be performed to test the potential of these substances to be used as novel antipruritic drugs.

Summary

Chronic itch is a common problem that can severely impair the quality of life of affected patients. In the skin and nervous system, complex cellular interactions can induce, exacerbate or suppress pruritus. Knowledge about the physiological and pathophysiological processes involved in the induction, perception, transmission and modulation of itch as well as about clinical characteristics of pruritus can help in identifying an optimal treatment for the patients. Unfortunately, currently available licensed treatment options are scarce, and off-label drugs are required in many cases. Novel antipruritic drugs are, however, on the way, and ongoing or planned clinical trials investigating the efficacy in reducing pruritus will hopefully provide us with safe and effective treatment alternatives for patients suffering from pruritus.

Questions and multiple choices

1. Which statement regarding chronic pruritus is correct?
   a. Chronic pruritus is a rare phenomenon
   b. Chronic pruritus is defined as pruritus persisting for 6 months or longer
   c. Up to 10% of patients with psoriasis suffer from chronic pruritus

d. The clinical classification of pruritus discriminates between primarily inflamed and primarily non-inflamed skin
e. The neuroanatomical classification is only used for pruritus originating in the CNS

2. Which cell **is not** involved in the development or maintenance of pruritus?
a. Eosinophil
b. Sensory nerve cell
c. Mast cell
d. Adipocyte
e. Keratinocyte

3. Which of the following statements regarding the development of pruritus is correct?
a. Keratinocyte-derived histamine plays an important role
b. The interaction between mast cells and nerve cells is of great importance
c. Fibroblasts and blood vessels are the main factors in triggering pruritus
d. Nerve cell damage is present in most cases of pruritus
e. Pruritus always develops in the skin

4. Which of the following statements **is not** correct?
a. Keratinocytes may be involved in the down modulation of pruritus by releasing endocannabinoids
b. Neutrophils are a major source of nerve growth factor
c. Mast cells are located in close vicinity to hair follicles, blood vessels, and sensory nerves
d. Various mast cell products, e.g. proteases, lipid mediators, cytokines, may be involved in the elicitation of pruritus
e. T cell-derived IL-31 can induce severe pruritus

5. Histamine is one of the major mediators of pruritus. Which of the following facts about histamine is true?
a. Histamine is a potent activator of mast cells
b. The major source of histamine in the skin are keratinocytes
c. There are currently 6 known histamine receptors
d. The H2 receptor is the receptor mainly responsible for pruritus
e. In addition to H1, H3 and H4 receptors can also modulate pruritus

6. Which sentence regarding the nervous system is correct?
a. Pruritus in the skin is mediated by myelinated Aβ-fibres
b. Pain stimuli often induce or exacerbate pruritus
c. Chronic stimulation of neuroreceptors leads to the reduction of the stimulation threshold of these receptors (peripheral sensitization)
d. Alloknesis and Hyperknesis typically occur in pain but not in pruritus
e. Levels of NGF are often found to be dramatically reduced in the skin of atopic dermatitis patients

7. Typical secondary skin changes can be found in some patients with chronic pruritus. These lesions do usually not include:
a. Erosions
b. Lichenification
c. Excoriations
d. Eczema
e. Hyper- or hypopigmentation

8. Many diseases of the skin are associated with pruritus, for which disease is this usually not the case?
a. Chronic spontaneous urticaria
b. Atopic dermatitis
c. Vitiligo
d. Cutaneous mastocytosis
e. Psoriasis

9. Which of the following therapies is not used in the management of pruritus?
a. Opiates
b. Antihistaminic agents
c. Anticonvulsive agents
d. UV-Therapy
e. Capsaicin cream

10. Which of the following therapeutic recommendations regarding the management of pruritus is correct?
a. Topical antihistamines are the first line therapy for chronic pruritus
b. Hot baths or showers can temporarily reduce pruritus and are therefore generally recommended on a daily basis
c. Moisturizing of the skin often enhances pruritus due to the occlusive effect
d. The use of antipruritic additives such as polidocanol, urea or menthol in topical applications should generally be avoided because of possible sensitizations
e. Certain foodstuffs, e.g. hot spices, alcohol or hot beverages can intensify the perception of itch

Correct Answers

1. d 6. c
2. d 7. d
3. b 8. c
4. b 9. a
5. e 10. e

References

1 Hafenreffer S. De Pruritu, in Nosodochium, in quo cutis, eique adhaerentium partium, affectus omnes, singulari methodo, et cognoscendi et curandi fidelissime traduntur. Ulm. Typis & expensis Balthasar. Kühnen. 1660: 98–102.
2 Ständer S, Weisshaar E, Mettang T *et al.* Clinical classification of itch: a position paper of the International Forum for the Study of Itch. *Acta Derm Venereol* 2007; **87**: 291–294.
3 Weisshaar E, Dalgard F. Epidemiology of itch: adding to the burden of skin morbidity. *Acta Derm Venereol* 2009; **89**: 339–350.
4 Dalgard F, Svensson A, Holm JO *et al.* Self-reported skin morbidity among adults: associations with quality of life and general health in a Norwegian survey. *J Investig Dermatol Symp Proc.* 2004; **9**: 120–125.
5 Matterne U, Strassner T, Apfelbacher CJ *et al.* Measuring the prevalence of chronic itch in the general population: development and validation of a questionnaire for use in large-scale studies. *Acta Derm Venereol* 2009; **89**: 250–256.

6 Twycross R, Greaves MW, Handwerker H *et al.* Itch: scratching more than the surface. *QJM* 2003; **96**: 7–26.
7 Pfab F, Valet M, Sprenger T *et al.* Temperature modulated histamine-itch in lesional and nonlesional skin in atopic eczema - a combined psychophysical and neuroimaging study. *Allergy* 2010; **65**: 84–94.
8 Yosipovitch G, Ishiuji Y, Patel TS *et al.* The brain processing of scratching. *J Invest Dermatol* 2008; **128**: 10806–11811.
9 Metz M, Maurer M. Innate immunity and allergy in the skin. *Curr Opin Immunol* 2009; **21**: 687–693.
10 Ständer S, Schneider SW, Weishaupt C *et al.* Putative neuronal mechanisms of sensitive skin. *Exp Dermatol* 2009; **18**: 417–423.
11 Stefansson K, Brattsand M, Roosterman D *et al.* Activation of proteinase-activated receptor-2 by human kallikrein-related peptidases. *J Invest Dermatol* 2008; **128**: 18–25.
12 Bigliardi PL, Tobin DJ, Gaveriaux-Ruff C *et al.* Opioids and the skin–where do we stand? *Exp Dermatol* 2009; **18**: 424–430.
13 Biró T, Tóth BI, Haskó G *et al.* The endocannabinoid system of the skin in health and disease: novel perspectives and therapeutic opportunities. *Trends Pharmacol Sci* 2009; **30**: 411–420.
14 Yamaura K, Oda M, Suwa E *et al.* Expression of histamine H4 receptor in human epidermal tissues and attenuation of experimental pruritus using H4 receptor antagonist. *J Toxicol Sci* 2009; **34**: 427–431.
15 Botchkarev VA, Metz M, Botchkareva NV *et al.* Brain-derived neurotrophic factor, neurotrophin-3, and neurotrophin-4 act as ''epitheliotrophins'' in murine skin. *Lab Invest* 1999; **79**: 557–572.
16 Metz M, Botchkarev VA, Botchkareva NV *et al.* Neurotrophin-3 regulates mast cell functions in neonatal mouse skin. *Exp Dermatol* 2004; **13**: 273–281.
17 Zhu Y, Wang XR, Peng C *et al.* Induction of leukotriene B(4) and prostaglandin E(2) release from keratinocytes by protease-activated receptor-2-activating peptide in ICR mice. *International immunopharmacology* 2009; **9**: 1332–1336.
18 Metz M, Lammel V, Gibbs BF *et al.* Inflammatory murine skin responses to UV-B light are partially dependent on endothelin-1 and mast cells. *Am J Pathol* 2006; **169**: 815–822.
19 Metz M, Grimbaldeston MA, Nakae S *et al.* Mast cells in the promotion and limitation of chronic inflammation. *Immunol Rev* 2007; **217**: 304–328.
20 Metz M, Maurer M. Mast cells–key effector cells in immune responses. *Trends Immunol* 2007; **28**: 234–241.
21 Cowden JM, Zhang M, Dunford PJ *et al.* The histamine H4 receptor mediates inflammation and pruritus in Th2-dependent dermal inflammation. *J Invest Dermatol* 2010; **130**: 1023–1033.
22 Sugimoto Y, Iba Y, Nakamura Y *et al.* Pruritus-associated response mediated by cutaneous histamine H3 receptors. *Clin Exp Allergy* 2004; **34**: 456–459.
23 Siebenhaar F, Magerl M, Peters EM *et al.* Mast cell-driven skin inflammation is impaired in the absence of sensory nerves. *J Allergy Clin Immunol* 2008; **121**: 955–961.
24 Raap U, Braunstahl GJ. The role of neurotrophins in the pathophysiology of allergic rhinitis. *Curr Opin Allergy Clin Immunol* 2010; **10**: 8–13.
25 Yamaguchi J, Aihara M, Kobayashi Y *et al.* Quantitative analysis of nerve growth factor (NGF) in the atopic dermatitis and psoriasis horny layer and effect of treatment on NGF in atopic dermatitis. *J Dermatol Sci* 2009; **53**: 48–54.
26 Bilsborough J, Leung DY, Maurer M *et al.* IL-31 is associated with cutaneous lymphocyte antigen-positive skin homing T cells in patients with atopic dermatitis. *J Allergy Clin Immunol* 2006; **117**: 418–425.
27 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* 2006; **117**: 411–417.
28 Grimstad O, Sawanobori Y, Vestergaard C *et al.* Anti-interleukin-31-antibodies ameliorate scratching behaviour in NC/Nga mice: a model of atopic dermatitis. *Exp Dermatol* 2009; **18**: 35–43.
29 Nakano T, Andoh T, Lee JB *et al.* Different dorsal horn neurons responding to histamine and allergic itch stimuli. *Neuroreport* 2008; **19**: 723–726.
30 Liu Q, Tang Z, Surdenikova L *et al.* Sensory neuron-specific GPCR Mrgprs are itch receptors mediating chloroquine-induced pruritus. *Cell* 2009; **139**: 1353–1365.
31 Sun YG, Chen ZF. A gastrin-releasing peptide receptor mediates the itch sensation in the spinal cord. *Nature* 2007; **448**: 700–703.
32 Carstens EE, Carstens MI, Simons CT *et al.* Dorsal horn neurons expressing NK-1 receptors mediate scratching in rats. *Neuroreport* 2010; **21**: 303–308.
33 Ständer S, Siepmann D, Herrgott I *et al.* Targeting the neurokinin receptor 1 with aprepitant: A novel antipruritic strategy. *PLoS ONE* 2010; **5**: e10968.
34 Ko MC, Naughton NN. An experimental itch model in monkeys: characterization of intrathecal morphine-induced scratching and antinociception. *Anesthesiology* 2000; **92**: 795–805.
35 Horta ML, Morejon LC, da Cruz AW *et al.* Study of the prophylactic effect of droperidol, alizapride, propofol and promethazine on spinal morphine-induced pruritus. *Br J Anaesth* 2006; **96**: 796–800.
36 Ko MC, Song MS, Edwards T *et al.* The role of central mu opioid receptors in opioid-induced itch in primates. *J Pharmacol Exp Ther* 2004; **310**: 169–176.
37 Toyoda M, Nakamura M, Makino T *et al.* Nerve growth factor and substance P are useful plasma markers of disease activity in atopic dermatitis. *Br J Dermatol* 2002; **147**: 71–79.
38 Ikoma A, Steinhoff M, Ständer S *et al.* The neurobiology of itch. *Nat Rev Neurosci* 2006; **7**: 535–547.
39 van Laarhoven AI, Kraaimaat FW, Wilder-Smith OH *et al.* Generalized and symptom-specific sensitization of chronic itch and pain. *J Eur Acad Dermatol Venereol* 2007; **21**: 1187–1192.
40 Schmelz M. Itch and pain. *Neurosci Biobehav Rev* 2010; **34**: 171–176.
41 Ikoma A, Handwerker H, Miyachi Y *et al.* Electrically evoked itch in humans. *Pain* 2005; **113**: 148–154.
42 Ständer S (ed.). Klassifikation und Klinische Charakteristika von Pruritus. In *Pruritus Bremen Uni-Med Science*, 2008; 16–19.
43 Ständer S, Streit M, Darsow U *et al.* Diagnostic and therapeutic procedures in chronic pruritus. *J Dtsch Dermatol Ges* 2006; **4**: 350–370.
44 Papoiu AD, Yosipovitch G. Topical capsaicin. The fire of a 'hot' medicine is reignited. *Expert Opin Pharmacother* 2010; **11**: 1359–1371.
45 Ständer S, Schürmeyer-Horst F, Luger TA *et al.* Treatment of pruritic diseases with topical calcineurin inhibitors. *Ther Clin Risk Manag* 2006; **2**: 213–218.
46 Dvorak M, Watkinson A, McGlone F *et al.* Histamine induced responses are attenuated by a cannabinoid receptor agonist in human skin. *Inflamm Res* 2003; **52**: 238–245.
47 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* 2008; **22**: 73–82.
48 Zuberbier T, Asero R, Bindslev-Jensen C *et al.* EAACI/GA(2)LEN/EDF/WAO guideline: management of urticaria. *Allergy* 2009; **64**: 1427–1443.
49 Thurmond RL, Gelfand EW, Dunford PJ. The role of histamine H1 and H4 receptors in allergic inflammation: the search for new antihistamines. *Nat Rev Drug Discov* 2008; **7**: 41–53.
50 Vasiadi M, Kalogeromitros D, Kempuraj D *et al.* Rupatadine inhibits proinflammatory mediator secretion from human mast cells triggered by different stimuli. *Int Arch Allergy Immunol* 2010; **151**: 38–45.
51 Weller K, Maurer M. Desloratadine inhibits human skin mast cell activation and histamine release. *J Invest Dermatol* 2009; **129**: 2723–2726.
52 Bergasa NV, McGee M, Ginsburg IH *et al.* Gabapentin in patients with the pruritus of cholestasis: a double-blind, randomized, placebo-controlled trial. *Hepatology* 2006; **44**: 1317–1323.

53 Taylor CP. Mechanisms of analgesia by gabapentin and pregabalin–calcium channel alpha2-delta [Cavalpha2-delta] ligands. *Pain* 2009; **142**: 13–16.
54 Mettang M, Weisshaar E. Pruritus: control of itch in patients undergoing dialysis. *Skin Therapy Lett* 2010; **15**: 1–5.
55 Phan NQ, Bernhard JD, Luger TA *et al.* Antipruritic treatment with systemic mu-opioid receptor antagonists: A review. *J Am Acad Dermatol* 2010; [Epub ahead of print].
56 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* 2010; **25**: 1251–1257.
57 Zylicz Z, Krajnik M, Sorge AA *et al.* Paroxetine in the treatment of severe non-dermatological pruritus: a randomized, controlled trial. *J Pain Symptom Manage* 2003; **26**: 1105–1112.
58 Zylicz Z, Smits C, Krajnik M. Paroxetine for pruritus in advanced cancer. *J Pain Symptom Manage* 1998; **16**: 121–124.
59 Davis MP, Frandsen JL, Walsh D *et al.* Mirtazapine for pruritus. *J Pain Symptom Manage* 2003; **25**: 288–291.
60 Shohrati M, Tajik A, Harandi AA *et al.* Comparison of hydroxyzine and doxepin in treatment of pruritus due to sulfur mustard. *Skinmed* 2007; **6**: 70–72.
61 Baldo A, Sammarco E, Plaitano R *et al.* Narrowband (TL-01) ultraviolet B phototherapy for pruritus in polycythaemia vera. *Br J Dermatol* 2002; **147**: 979–981.
62 Hsu MM, Yang CC. Uraemic pruritus responsive to broadband ultraviolet (UV) B therapy does not readily respond to narrowband UVB therapy. *Br J Dermatol* 2003; **149**: 888–889.
63 Darsow 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* 2010; **24**: 317–328.
64 Tominaga M, Ogawa H, Takamori K. Possible roles of epidermal opioid systems in pruritus of atopic dermatitis. *J Invest Dermatol* 2007; **127**: 2228–2235.
65 Dunford PJ, Williams KN, Desai PJ *et al.* Histamine H4 receptor antagonists are superior to traditional antihistamines in the attenuation of experimental pruritus. *J Allergy Clin Immunol* 2007; **119**: 176–183.
66 Duval A, Dubertret L. Aprepitant as an antipruritic agent? *N Eng J Med* 2009; **361**: 1415–1416.

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