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Therapy of Pruritus

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Abstract

Importance of the field—Pruritus is the predominant symptom of skin disease. Due to the poorly understood pathophysiology, the development of effective treatment modalities for pruritus has proven to be particularly difficult. At present, there is no universally accepted therapy for itch. The purpose of this review is to provide an update on the treatment of pruritus.

Areas covered in this review—An overview of current, emerging and possible future therapies for pruritus is provided.

What the reader will gain—Insights into possible treatment regimes for pruritus in different clinical scenarios.

Take home message—The therapy of pruritus is challenging and currently takes on an individualistic approach. Recent advancements in the mechanisms that underlie this distressing symptom have identified novel targets for future therapy

Keywords

pruritus; antipruritics; itching; skin disease

1. Introduction

Pruritus (itching) is the most common symptom of skin disease and can best be defined as an unpleasant sensation that leads to a desire to scratch.[1-3] It can also be a lead symptom in systemic and psychiatric disorders.[4, 5] All human beings experience pruritus in the course of their lifetime; therefore, it is important to make a distinction between acute itch, which is of a limited period of time ranging from seconds to a week such as the itch related to acute insect bite reaction, and chronic itch, which lasts for greater than 6 weeks and the treatment of which will be the focus of this review.[6] Pruritus has a profound impact on quality of life through disturbances related to sleep, attention, and sexual function, to name but a few.[7-9] In addition, studies have shown hemodialysis patients who itch have an increased mortality.[4, 10] Furthermore, chronic pruritus is an enormous burden to society through treatment-related costs, which is particularly great due to the high rate of therapeutic failure.[11]

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The management of pruritus is challenging especially when an underlying etiology cannot be identified. Due to the poorly understood pathophysiology, the development of effective treatment modalities for pruritus has proven to be particularly difficult. At present, there is no universally accepted therapy for itch. Instead, management of pruritus takes an individualistically tailored approach. Recent advancements in the pathophysiology of pruritus however has renewed interest in this distressing symptom and identified novel targets for therapy. The purpose of this review is to provide an overview of current, emerging and possible future therapies for pruritus.

2. General Principles in the Treatment of Pruritus

There are a number of possible underlying etiologies for pruritus (Table 1). A detailed history and physical examination are thus of prime importance in the treatment of pruritus. It assists in the identification of a possibly underlying cause and allows a more focused treatment plan to be instituted. If an underlying cause is discovered it should be treated as pruritus frequently improves when the underlying disease is addressed. Topical therapies are the mainstay of therapy for mild and localized itch while systemic therapies should be considered for severe and generalized itch.

3. Topical Treatments of Pruritus

An overview of topical treatments of pruritus is provided in table 2.

3.1 Moisturizers, Emollients and Barrier Creams

Moisturizers, emollients and barrier repair creams are the cornerstone of antipruritic treatment often reducing pruritus through improved barrier function. Transepidermal water loss (TEWL) is reflective of the epidermal barrier function and has been associated with itch intensity in patients with atopic dermatitis.[12] This observation may be explained by the suboptimal epidermal barrier function facilitating the entry of irritants and itch-causing agents. Interestingly, TEWL has been shown to be increased at night and thus topical therapies that provide an occlusive film may be particularly useful for nocturnal pruritus as well as those with dry or atopic skin.[13, 14]

Recent studies have suggested serine proteases, via activation of protease-activating receptor 2 (PAR_2) located on C fiber terminals, may play an important role in mediating pruritus.[15, 16] Topical therapies with a low pH may reduce pruritus through a reduction in activity of the serine protease such as mast cell tryptase (an endogenous PAR_2 agonist). In addition, topical therapies with a low pH may be especially useful in optimizing the skin barrier function through their maintenance of the normal acidic pH of the skin surface.

3.2 Topical Corticosteroids

Topical corticosteroids should only be used to provide relief of itching associated with inflammatory skin diseases such as atopic dermatitis or psoriasis. However, they should not be used to treat generalized chronic itch or for prolonged periods. Corticosteroids are not directly antipruritic and it is believed they exert a beneficial effect on pruritus through their reduction in skin inflammation. It has been shown that 2.5 % hydrocortisone significantly decreases experimentally induced pruritus when compared to placebo.[17] Although higher strengths of corticosteroid have greater efficacies, there is also an increased risk of side-effects (e.g. skin atrophy, telangiectasia, and hypothalamus-pituitary axis suppression).

3.3 Topical Immunomodulators

The topical calcineurin inhibitors (TCI), tacrolimus and pimecrolimus, have been shown to be effective in reducing pruritus in atopic dermatitis patients.[18, 19] Reports of other pruritic dermatoses treated successfully with topical calcineurin inhibitors include chronic irritative hand dermatitis, graft-versus host disease, lichen sclerosis, anogenital pruritus and prurigo nodularis.[20] Common side effects of these agents are transient burning and stinging sensations. The mechanism underlying this reduction in pruritus seen with TCIs is unclear. It is possible that the anti-inflammatory properties of these agents mediate their antipruritic effects. However, recent evidence has implicated the transient-receptor potential vanilloid receptor-1 (TRPV1) located on nerve fibers as having a role to play in the reduction of pruitus seen with TCIs.[18, 19, 21-23] Of note, TRPV1 has been recently implicated in the pathogenesis itch via the activation of phospholipase A2 and 12-lipoxygenase.[24]

3.4 Topical Antihistamines

Doxepin, a tricyclic antidepressant, is a potent H_1 and H_2 antagonist. Doxepin 5% cream has been shown to significantly reduce pruritus in patients with atopic dermatitis, lichen simplex chronicus, contact dermatitis and nummular dermatitis.[25, 26] However, drowsiness, through systemic absorption of doxepin, occurs in approximately 20 -25% of patients, limiting its use especially in children. Other common side effects of this treatment include localized cutaneous burning and allergic contact dermatitis.[25, 26]

3.5 Menthol

Menthol has been used alone or in combination as a topical antipruritic for centuries. Menthol elicits the same cool sensation as low temperature through the TRPM8 receptor, a member of the transient receptor potential (TRP) family of excitatory ion channels.[27, 28] Cooling the skin and menthol both result in the relief of experimentally induced itch, although the latter is not associated with a decrease in skin temperature.[29] This has lead to menthol at concentrations of 1 – 3 % being commonly used to relieve pruritus while higher doses can induce irritation. Of note, patients who report a reduction in pruritus with cold sensation may especially benefit from topical therapies containing menthol.[30]

3.6 Capsaicin

Topical capsaicin acts through TRPV1 expressed on sensory skin nerves to release neuropeptides such as substance P.[31, 32] TRPV1 recently has been implicated in the pathogenesis of pruritus and thus may be the target through which capsaicin exerts its antipruritic effect.[33] Beneficial effects of capsaicin have been reported in chronic, localized pruritic disorders, particularly those of neuropathic origin, such as notalgia paresthetica and brachioradial pruritus as well as other pruritic conditions (e.g. prurigo nodularis, aquagenic pruritus and pruritus associated with chronic kidney disease).[34-38] Initial application causes an intense transient burning sensation at the application site which may lead to poor compliance or premature cessation of treatment; however, this side effect usually resolves after using the medication for a few days or with application of a topical anesthetic.[39] A recent study suggests that African Americans display a notably limited hyperalgesia and neurogenic inflammation in response to topical capsaicin suggesting that response to certain anti-pruritic agents may differ between ethnic populations.[40]

3.7 Local anesthetics

Topical local anesthetics such as pramoxine 1 percent, lidocaine 5 percent and the eutectic mixture of lidocaine 2.5 percent and prilocaine 2.5 percent, have all been shown to have antipruritic properties.[41-43] In a randomized double-blind, controlled comparative trial, pramoxine-based anti-itch lotion was shown to be more effective than a control lotion for the

treatment of pruritus in adult hemodialysis patients.[44] Interestingly, intravenous lidocaine has recently been reported to ameliorate the severity of pruritus in a case series of patients with chronic cholestatic liver diseases.[45] Polidocanol is a non-ionic surfactant with both local anesthetic properties and moisturizing effects. In an open-label study, a combination of 5 percent urea and 3 percent polidocanol was found to significantly reduce pruritus in patients with atopic dermatitis, contact dermatitis, and psoriasis.[46]

3.8 Topical salicylic acid

Topical acetylsalicylic acid, a cyclooxygenase inhibitor, has been shown to significantly reduce pruritus in a double-blind, crossover placebo trial in patients with lichen simplex chronicus, however, oral salicylates do not relieve pruritus except in polycythemia vera.[47] Prostanoids, encompassing the prostaglandins (PG) and the thromboxanes (TX), are the cyclooxygenase products of arachidonic acid. Importantly, TXA_2 has recently been shown to induce itch-associated responses through its thromboxane-prostanoid (TP) receptors located in both keratinocytes as well as skin nerve fibers in mice. This response was abolished by deficiency of the TP receptor and a TP receptor antagonist.[48] It is possible that the antipruritic actions of topical acetylsalicylic acid may in part be explained by their inhibitory effects on prostanoids.

3.9 Topical Cannabinoids

It has recently been shown that both cannabinoid receptors CB_1 and CB_2 are expressed on cutaneous sensory nerve fibers, mast cells and keratinocytes.[49] This was followed by the observation that peripheral administration of a cannabinoid receptor agonist attenuates histamine-induced itch in humans.[50] Subsequently, the CB_2 agonist, N-palmitoylethanolamine has been incorporated into creams with relief of pruritus reported in patients with atopic dermatitis, lichen simplex, prurigo nodularis and chronic kidney disease-associated pruritus.[51-53] These promising preliminary results leads one to believe that new therapies that target cannabinoid receptors may lead to the development of effective antipruritic treatments in the future.

4. Systemic Treatments of Pruritus

An overview of systemic treatments of pruritus is provided in table 3.

4.1 Antihistamines

Oral antihistamines have traditionally been the cornerstone of pruritus treatment. With the exception of urticaria, antihistamines have little effect on conditions associated pruritus. However, sedating (first-generation) antihistamines may have a role in patients where pruritus is exacerbated at night probably via their soporific effects.[14] In cases of urticaria, sedative antihistamines, such as hydroxyzine, may be particularly valuable with pruritus during the night while non-sedating (second-generation) antihistamines such as loratadine, desloratadine, cetirizine and levocetirizine may be suitable in the daytime for relief of pruritus.

4.2 Antidepressants

The selective neuroepinephrine re-uptake inhibitor (SNRI), mirtazapine, has been reported to relieve itch in patients with advanced cancer, leukemia, lymphoma (including cutaneous lymphoma), chronic kidney disease, cholestasis and atopic dermatitis.[54-56] Mirtazapine acts as an antagonist at noradrenergic α_2-receptors and 5-HT_2 and 5-HT_3 serotonin receptors, increasing central noradrenergic and 5-HT_1 serotonergic neurotransmission.[57, 58] It also has a sedative effect through its H_1-antihistamine properties. Which of these mechanisms mediates the antipruritic properties of mirtazapine is still unclear but it has been suggested medications interfering with neuronal reuptake of neurotransmitters such as serotonin and norepinephrine

may act through the cerebral cortex to reduce the perception of pruritus.[59] Mirtazapine is a relatively safe medication without serious side effects and may be an especially useful for the treatment of nocturnal pruritus.[55] The new SNRIs such as venlafaxine and duloxetine do not seem to have significant antipruritic effects in our experience.

Selective serotonin re-uptake inhibitors (SSRIs) may also have antipruritic effects. In an open-labeled study, the SSRIs, paroxetine and fluvoxamine, were shown to reduce pruritus in 68 per cent of patients with chronic pruritus, with the most favourable responses being seen in patients with pruritus due to atopic dermatitis, systemic lymphoma and solid carcinoma.[60] Sertraline, another SSRI, has also been shown to an effective, well-tolerated treatment for pruritus due to chronic liver disease.[61]

4.3 Opioid Agonists and Antagonists

An imbalance of the endogenous opioidergic system has recently been implicated in the pathophysiology of pruritus. It is believed that μ- and κ-opioid receptor agonists may act inversely in terms of their pruritic properties – μ-opioid receptor agonists and κ-opioid receptor antagonists induce itch, while μ-receptor antagonists and κ-receptor agonists reduce it.[62-64] This concept was founded on the observations that the well-known side effect of pruritus, caused by analgesic medications that act as μ-opioid recptor agonists, is reversed by μ-opioid receptor antagonists.[65] In addition, κ-opioid receptor agonists reduce pruritus.[63] This has lead to the opioidergic system being targeted by new antipruritic medications.

Several studies have shown the antipuritic effects of μ-opioid receptor antagonists such as naltrexone and nalmefene. Natrexone has been reported to reduce pruritus in patients with cholestasis, end-stage renal disease, burns and atopic dermatitis.[66-69] However, its widespread use has been limited due a high rate of initial adverse effects and cost. Double blind, placebo-controlled studies have also shown a reduction in pruritus through treatment with nalmefene in patients with cholestasis, atopic dermatitis and urticaria.[70, 71]

The κ-opioid receptor agonists butorphanol and nalfurafine appear to be beneficial in pruritic conditions. Butorphanol has been reported in a case series of 5 patients to be effective in the treatment of chronic intractable itch associated with inflammatory skin diseases or systemic diseases when administered intranasally at concentrations of 1 mg once a day.[72] In addition, recent results of a Phase III, double-blind, placebo-controlled study involving 337 patients with chronic kidney disease associated-pruritus showed that orally taken nalfurafine effectively reduced itch.[73] Of note, nalfurafine has been officially approved for clinical use as an antipruritic for chronic kidney disease associated-pruritus in Japan since January 2009.

4.4 Neuroleptics

Gabapentin and pregablin are structural analogs of the neurotransmitter γ-aminobutyric acid (GABA). The exact mechanisms of their antipruritic effects are not clear but may be related to the hindrance of nociceptive sensations to the brain and thus pruritus. Gabapentin may be particularly useful in forms of neuropathic pruritus related to nerve entrapment disorders such as brachioradial pruritus and notalgia paresthetica.[74,75]

Additionally, it has been demonstrated that 300 mg of oral gabapentin taken after each hemodialysis session was a safe and effective treatment option for CKD-associated pruritus through a randomized, placebo-controlled double-blind trial.[76] Of note, the renal excretion of gabapentin is reduced in dialysis patients and thus it has been suggested that using a lower dose of gabapentin (100 mg after each hemodialysis session under nurse surveillance), with slow upward titration may reduce the risk of gabapentin-induced neurotoxicity and/or coma in patients with reduced renal function.[77] Gabapentin has also been reported to be particularly

valuable in the treatment of pruritus associated with cutaneous lymphoma in a case series.[56] Surprisingly, a placebo-controlled double-blind study showed gabapentin not to be beneficial in pruritus of cholestasis; in fact, it was associated with an increase in the perception of pruritus and scratching in some patients, thus should be avoided in this patient population.[78]

Pregabalin has been shown to have a beneficial effect on chronic pruritus through a case series of 3 patients. Treatment should not be stopped abruptly due to the risk of withdrawal symptoms.[79]

4.5 Substance P Antagonist

Aprepitant, an oral antiemetic drug that antagonizes the effect of substance P on neurokinin type 1 receptor, has recently been shown to be effective against pruritus associated with the Sézary syndrome in a case series of 3 patients.[80] A major drawback for its current use in the US is that it is extremely expensive. Further data is needed to assess the efficacy of this agent as an antipruritic.

4.6 Immunosuppressants

The oral immunosuppressants, cyclosporine and azothioprine, have demonstrated antipruritic effects in patients with atopic dermatitis most likely through their anti-inflammatory effects. In a double-blind, randomized, placebo-controlled study, oral cyclosporin therapy was shown to decrease both itching and disease severity in atopic dermatitis.[81] The widespread use of this agent has been limited due to the risk of significant hypertension, elevated creatinine and blood urea nitrogen, immunosuppression and renal toxicity. Monotherapy with oral azathioprine in a double-blind, placebo-controlled study resulted in significant improvements in itch score, disease activity and quality of life in patients with atopic dermatitis.[82] Caution is advised when prescribing this medication due to the risk of dose-dependent myelotoxicity. The susceptibility of individuals to myelosuppression induced by azathioprine is known to relate to the activity of thiopurine methyl transferase (TPMT), a key enzyme in azathioprine metabolism. Thus, measurement of erythrocyte TPMT activity before initiation of therapy helps identify those patients at high risk of this serious side effect.[82, 83] In the experience of the authors, African Americans display lower enzyme activity and therefore extreme caution should be taken using this drug in these patients with intermediate levels of TPMT. It is recommended that oral cyclosporine and azathioprine, only be used in the short-term for patients with atopic dermatitis who have failed conventional therapy and with appropriate monitoring.

5. Possible Future Treatments of Pruritus

In the past the poorly understood pathophysiology of pruritus has impeded the development of effective antipruritic treatment. However, recent advancements in the mechanisms that underlie this distressing symptom have identified novel targets for therapy (Table 4). Given the possible role of the opioidergic system in pruritus, a preliminary study supported a role for the μ-opioid receptor antagonist, naltrexone, in a topical 1 % form in the treatment of severe pruritus.[84] The efficacy of topical methylnaltrexone on pruritus in larger studies will be of particular interest. Interestingly, in April 2008, the FDA approved subcutaneous methylnaltrexone for the treatment treatment of opioid induced constipation. Although subcutaneous methylnaltrexone has not been used as an antipruritic, it should in theory be of value in the treatment of pruritus.[85] Of note, methylnaltrexone does not cross the brain-barrier, offering the advantage of peripheral action only and thus significantly less adverse effects including addiction.

NGX-4010, a high-concentration capsaicin (8%) dermal patch has been shown to provide lasting relief of peripheral neuropathic pain and has been recently been approved by the FDA.

[86] Although this drug has not been used to treat pruritus, it should in theory be useful for the treatment of neuropathic itch.

Prostanoids have been implicated in the pathophysiology of pruritus. Prostaglandin D_2 (PGD_2) has been shown to play a role in inhibiting pruritus in mice models of atopic-like dermatitis.[87, 88] In addition, TS-022, a prostanoid DP_1 receptor agonist, has been shown to suppress scratching and improve the skin inflammation in mouse models of atopic dermatitis.[89] TS-022 is currently in Phase II trials for the treatment of pruritus in atopic dermatitis.

As mentioned previously, serine proteases, via activation of PAR_2, may have an important role in mediating pruritus. Thus, the development of topical medications that inhibit serine proteases or act as PAR_2 antagonists may be fruitful and lead to a new class of antipruritic therapy. Additionally, there is increasing recent evidence that interleukin (IL)–31 has a role in pruritus. It has been demonstrated that IL-31 act as an inducer of itch and dermatitis in mice, and that IL-31 is overexpressed in keratinocytes in atopic dermatitis.[90] Furthermore, IL-31 antibody could effectively reduce scratching behavior in an atopic dermatitis-like murine model during the onset of clinical skin manifestations. [91,92] These observations suggest a potential therapeutic role of IL-31 antibody in treatment of chronic itch.

6. Conclusion

An estimated 8% of the adult population suffers from chronic itch.[93] The therapy of pruritus is challenging and needs an individualistic approach. In the past, the development of antipruritics has been hampered by a poor understanding of the pathophysiology of this distressing symptom. In addition, the number of studies examining the efficacy of antipruritus is limited and most of the data available is based on case series or small-scale studies. Larger studies in the future would help delineate the efficacy of available and proposed antipruritics. It is hoped that recent advancements in the pathophysiology of pruritus will also drive the development of novel therapies for this often neglected symptom.

7. Expert Opinion

The management of chronic pruritus can be extremely challenging and an individualistic approach needs to be taken. There is currently a lack of large-placebo controlled trials as well as head-to-head trials involving antipruritics which is problematic. Many of the mentioned antipruritics are used “off-label” and are not FDA approved for this indication. In addition, pharmaceutical companies are reluctant to perform double-blind studies assessing the efficacy of these medications for pruritus and thus most reports are limited to case series or small study sizes. Furthermore, the varying pathogenesis for pruritus in different disorders means that a universally accepted therapy is difficult to establish. In fact, many times a patient with chronic pruritus may have more than one origin for their pruritus.

There are clinical scenarios where certain therapies may be especially valuable. Nocturnal pruritus can be a particular problem in most patients with generalized pruritus. We frequently use mirtazapine in such patients with good effect. In patients with intractable nocturnal itch, it is our experience that butorphanol may be particular valuable. The beneficial effects of these agents on pruritus may in part be explained by their sedative properties. For neuropathic pruritus, topical capsaicin or the oral neuroleptics, gabapentin or pregabalin, are often employed as first line agents. We have also found that topical calcineurin inhibitors to be particularly effective for anogenital pruritus. In patients who report pruritus to be ameliorated with cooling, menthol is often of value. Additionally, psychiatric patients who experience pruritus may find treatment with SNRIs or SSRIs especially beneficial. Furthermore, in our experience a combination of both bile salt–lowering and opioid antagonist strategies are part of the management of pruritus of cholestasis. Of note, one may use a combination of low dose

mirtzapine and pregabalin or gabapentin in patients with recalcitrant chronic pruritus.[94] This combination therapy targets the hypersensitization of nerve fibers that occurs in chronic itch sufferers.[95, 96]

Highlights Box

- Pruritus is the predominant symptom of skin disease
- Identifying the underlying cause of pruritus is of prime importance in order to tailor treatment plans
- At present, there is no universally accepted therapy for itch
- Topical therapies are the mainstay of therapy for mild and localized itch while systemic therapies should be considered for severe and generalized itch
- Recent advancements in the pathophysiology of pruritus has renewed interest in this distressing symptom and identified novel targets for potential future therapies

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Table 1

Common disorders causing pruritus

Skin disorders
Atopic dermatitis
Psoriasis
Urticaria
Systemic disorders
Chronic kidney disease
Chronic liver disease
Haematological disorders
e.g. Lymphoma
Endocrine disorders
e.g.Thyroid disease
Neuropathic disorders
Post-herpetic pruritus
Nerve entrapment disorders
Psychological disorders
Obsessive compulsive disorder
Depression
Substance Abuse

Table 2

Topical treatments of pruritus

MEDICATION	DOSE	NOTES
Barrier repair creams / moisturizers / emollients	Not applicable	Low pH products may be particularly useful
Topical corticosteroids	Variable	Not directly antipruritic, may be useful in pruritus due to inflammatory skin dermatoses
Topical calcineurin inhibitors	Tacrolimus 0.03% and 0.1% ointment Pimecrolimus 1% cream	Particularly useful in anogenital pruritus, may experience transient burning and stinging
Doxepin	5% cream	Avoid in children, 20-25 % risk of sedation
Menthol	1 – 3 % cream or lotion	Useful in patients who report cooling as an alleviating factor
Capsaicin	0.025%–0.1% cream	Particularly useful in neuropathic itch, may experience initial transient burning
Salicylic acid	2%–6%	Useful in lichen simplex chronicus, avoid in acute inflammatory dermatoses and children
Local anesthetics		
	Pramoxine 1.0%–2.5%	Useful for pruritus on face and that associated with CKD
	Lidocaine patch 5%	Useful in neuropathic pruritus
	Eutectic mixture of lidocaine 2.5% and prilocaine 2.5%	
	5% urea + 3% polidocanol (laurylmacrogol)	Both moisturising and anesthetic properties
Cannabinoids	Creams containing N-palmitoylethanolamine	Useful in atopic dermatitis and CKD-associated pruritus

Table 3

Systemic treatments of pruritus

MEDICATION	DOSE	NOTES
Antihistamines	Variable depending on medication	No direct effect on pruritus except in urticaria, sedating antihistamines may be useful through their soporific effects
Antidepressants		
SNRIs	Mirtazapine 7.5 - 15 mg PO qhs	Useful in nocturnal pruritus, may cause increased weight and appetite
SSRIs	Paroxetine 10 mg - 40 mg PO qd	Consider in psychiatric patients with pruritus and paraneoplastic pruritus
	Fluvoxamine 25 -150 mg PO qd	Consider in psychiatric patients with pruritus and paraneoplastic pruritus
	Sertraline 75 -100 mg PO qd	Useful in cholestatic pruritus
μ-opioid receptor antagonists	Naltrexone 25 – 50 mg PO qd	Useful in patients with cholestatic and CKD-associated pruritus, may cause nausea, vomiting and drowsiness
κ-opioid receptor agonists	Butorphanol 1 – 4 mg intranasally qd	Useful in nocturnal and intractable pruritus, may cause nausea and vomiting as well as drowsiness
	Nalfurafine 2.5 - 5 μg PO qd	Useful in CKD-associated pruritus, may cause insomnia, approved in Japan only
Neuroleptics	Gabapentin 100 – 3600 mg PO qd	Useful in neuropathic pruritus, may cause drowsiness and weight gain
	Pregablin 150 – 300 mg PO qd	
Substance P antagonist	Aprepitant 80 mg PO qd	Benefical in pruritus associated with the Sézary syndrome, expensive
Immunosuppressants	Cyclosporin 2.5 – 5 mg/kg PO qd	Consider in atopic dermatitis patients with treatment refractory pruritus, monitor blood pressure and renal function, short term use
	Azathioprine 2.5 mg/kg PO qd	Consider in atopic dermatitis patients with treatment refractory pruritus, monitor for myelosuppression

Table 4

Possible Future Treatments of Pruritus

Methylnaltrexone
μ-opioid receptor antagonist
Topical or subcutaneous
NGX-4010
High-concentration capsaicin (8%) dermal patch
Neuropathic pruritus
TS-022
Prostanoid DP1 receptor agonist
Phase II trial for treatment of pruritus in atopic dermatitis
Serine proteases/PAR_2 antagonists
IL-31 antibody