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REVIEW ARTICLE

# PERSPECTIVES IN THE TREATMENT OF PRURITUS: FOCUS ON NEW STRATEGIES

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**SUMMARY**

*Pruritus is a common symptom and the main source of morbidity in dermatologic diseases. Current management has been hampered by our inadequate understanding of the pathomechanisms of pruritus, but recent advances in elucidating the mediators, receptors and neuronal pathways hold promise for the development of new translational therapies. These mediators and receptors in the skin, peripheral nerves, spinal cord and brain form markers that drugs can be directed to inhibit via itch-transmitting pathways. Such targeted therapy is likely to be more effective and produce less side effects. Clinically, the treatment of pruritus should be tailored for different pruritic diseases, individualized for different patients and instituted early before the development of central sensitization. Chronic pruritus is a multidimensional problem and management requires a holistic approach, addressing the peripheral skin and neuronal pathologies, aberrant central processes and psychosocial factors.*

## INTRODUCTION

Itch is a common symptom and the main source of morbidity in dermatologic diseases. In a study conducted in Norway, 8.4% of 18,770 adults in the general population reported having itch during the previous week (1). Pruritic skin diseases are associated with a high level of psychosocial morbidity, with patients frequently reporting depressive symptoms, sleep disturbances, agitation, concentration problems, and even changes in sexual functioning and eating habits (2-5). The treatment of itch, however, has so far been suboptimal and options are limited. This therapeutic inefficacy can mainly be attributed to our inadequate understanding of the pathophysiology of itch.

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Major advances in recent years, however, have elucidated the neuronal pathways and many mediators involved in itch signaling. A targeted, tailored and holistic approach would be a promising strategy to enhance our therapeutic capability in this field.

## DIRECTED THERAPIES

With better understanding of the physiological and pathological mechanisms of itch transmission and processing, using treatments directed at specific parts of the signaling pathways provides promise for more effective antipruritic treatment (Table I). As compared to nonspecific peripherally blocking and central inhibitory agents, directed therapy also tends to produce fewer side effects, as only itch signaling pathways are targeted and inhibited.

### Targeting the skin and peripheral nerves

Keratinocytes are our first channel of communication with our environment. It is not surprising that neuropeptides, neurotransmittors and their receptors are found in these cells, which allow them to communicate with nerve fibers to convey noxious sensations, such as itch, to the brain. Other immune cells in the dermis are also involved in the initiation of itch, and these include mast cells, eosinophils and T cells.

Histamine, which is secreted by mast cells and keratinocytes, has been the prototypical pruritogen for decades. $H_1$ receptor antihistamines, the sole antipruritic treatment until recently, have not been useful for most types of pruritus, except for urticaria, insect bites and allergic drug eruptions. The discovery of the histamine $H_4$ receptor in 2000 (6) and evidence for its role in allergic inflammation and pruritus have recently rekindled interest in developing antihistamines to treat itch (7-10). The efficacy of the $H_4$ receptor antagonist JNJ-7777120 has been encouraging in models of pruritus, asthma and allergic rhinitis (11-13) and substance P-induced itch (14), and clinical studies are currently ongoing to develop it as a novel antipruritic treatment. Its effect on Th2 cell-mediated inflammation, in addition to pruritus, further suggests that it is a promising treatment for atopic dermatitis (AD) (15).

A distinct signaling pathway involving activation of peripheral and spinothalamic neurons by a plant known as cowhage has been discovered recently (16, 17). Increased levels of the protease-activated

***Table I.*** *Emerging and potential targeted antipruritic agents.*

| Mediator/receptor | Mechanism | Drug |
|---|---|---|
| Histamine $H_4$ receptor | Antagonist | JNJ-7777120 |
| Protease-activated receptor PAR2 | Inhibitor<br>Antibody<br>Antagonist | Tetracyclines |
| Serine proteases | Inhibitor | Nafamostat mesilate<br>Camostat mesilate |
| Cathepsin S | Inhibitor | |
| Interleukin-31 | Antibody | |
| μ Opioid receptor | Topical antagonist<br>Peripherally active antagonist | 1% Naltrexone cream<br>Methylnaltrexone<br>Alvimopan |
| κ Opioid receptor | Topical agonist (also a μ opioid receptor antagonist)<br>Peripherally active agonist | Butorphanol (liposomal formulation)<br>ICI-204448 |
| Transient receptor potential channel TRPV1 | Ligand<br>Activator | Transdermal 8% capsaicin (Qutenza®)<br>Tacrolimus |
| Transient receptor potential channel TRPV3 | Inhibitor | |
| Cannabinoid receptor | Fatty-acid amide hydrolase inhibitor | |
| Nerve growth factor | Antibody | |
| High-affinity nerve growth factor receptor TrkA | Inhibitor | |
| Acetylcholine | Inhibitor | Botulinum toxin (subcutaneous and topical) |
| Mas-related G-protein coupled receptor (MRGPRX) | Antagonist | |
| Lysophosphatidic acid and autotaxin | Inhibitors (in cholestatic pruritus) | |
| Substance P | Inhibitor | |
| Tachykinin $NK_1$ receptor | Antagonist | Aprepitant |
| Gastrin-releasing peptide | Antibody | |
| Gastrin-releasing peptide receptor | Antagonist | |

receptor PAR2, the receptor for cowhage, were found in AD lesions (18), and this protease pathway is likely to play an important role in chronic pruritic diseases. A therapeutic approach would be to inhibit the endogenous components of this pathway, which consists of proteases such as serine protease and cathepsin S [19]) and PAR2. Serine protease signaling through PAR2 was also found to be involved in epidermal barrier function (20) and skin inflammation (21), and therefore serine protease inhibitors and PAR2 receptor antagonists are potential treatments for conditions such as AD and pruritus of advanced aging.

Nafamostat mesilate and camostat mesilate are synthetic serine protease inhibitors that are reported to be effective in refractory chronic urticaria (22). The former, which has been used as an anticoagulant, was also shown to effectively inhibit scratching in an AD mouse model (23). Tetracyclines, which were shown to reduce the PAR2-mediated production of interleukin-8 by keratinocytes (24), can potentially be useful in pruritic inflammatory conditions such as pruritic acne vulgaris and bullous pemphigoid, by reducing both pruritus per se and inflammation by antagonizing PAR2. Anti-PAR2 antibodies and PAR2 receptor antagonists have been used to inhibit itch induced by tryptase and in models of AD and chronic dry skin in mice (23, 25, 26). An inhibitor of cathepsin S has also been used in laboratory studies to inhibit itch signaling (19, 27).

Interleukin-31 (IL-31) is the most recent inflammatory cytokine found to mediate pruritus (28). Its role in inducing scratching and dermatitis in mice (29) and in the pathogenesis of AD and prurigo nodularis lesions (30), together with the efficacy of an anti-IL-31 antibody in reducing scratching in an AD mouse model (31), have created excitement with regard to its potential as a new agent for treating AD and other pruritic inflammatory skin diseases. In addition, mutations in the IL-31 receptor have recently been implicated in the pathogenesis of itch in familial primary cutaneous amyloidosis, an inherited localized cutaneous disease (32, 33).

The efficacy of opioid receptor agonists and antagonists in treating numerous types of pruritic diseases has been demonstrated in multiple studies (34-39). Increasing evidence suggests that the opioid system is functional in the skin, in addition to the central nervous system (40). Peripherally acting opioid receptor agonists and antagonists, which do not cross the blood–brain barrier, may be alternatives to the centrally acting agents that produce significant side effects. Methylnaltrexone and alvimopan are peripherally acting μ opioid receptor antagonists approved for use in the U.S. for improving gut motility in various clinical settings. Methlynaltrexone was found to improve morphine-induced pruritus (41) and has been used to treat intraspinal and epidural analgesia-associated itch (42). A peripherally acting κ opioid receptor agonist, ICI-204448, was also previously reported to prevent chloroquine-induced itch in mice (43). The above-mentioned agents may potentially be a new class of antipruritic agent. Topical opioid receptor agonists/antagonists have also been developed. Naltrexone 1% cream was found to be effective in pruritus of AD in two studies (44) and a topical liposomal butorphanol preparation was able to provide sustained drug release into the systemic circulation over 24 hours (45). The main utility of these topical agents would be for localized pruritic conditions and more trials are required to demonstrate their clinical utility.

Transient receptor potential TRPV1 channels are expressed on sensory neurons and non-neuronal cells (46). Activation causes excitation of C-fibers, the release and subsequent depletion of neuropeptides, a mechanism whereby capsaicin is used to alleviate pain and itch (47, 48). Qutenza®, a new high-potency transdermal formulation of 8% capsaicin, has recently been approved in the U.S. and Europe for the treatment of post-herpetic neuralgia, and it was shown to be superior to a lower-concentration formulation for the treatment of various types of neuropathic pain (49). In addition, in contrast to the usual 0.025% to 0.1% capsaicin cream, a single 30- or 60-minute application was able to provide pain relief for up

to 3 months, with minimal adverse effects. This formulation is also likely to be effective in neuropathic itch and can be used for more symptomatic cases. Initial burning sensation is the main side effect of capsaicin and pre- or concurrent application of a local anesthetic agent may improve compliance (50). Tacrolimus, a calcineurin inhibitor, is another agent that inhibits pruritus through its effects on TRPV1. Unlike capsaicin, which binds to TRPV1 directly, tacrolimus was shown to promote phosphorylation of TRPV1, cause inactivation of calcium channels and result in desensitization of neurons (51).

The TRPV3 channel is another member of the transient receptor potential channel family and TRPV3 transgenic mice with a Gly573Ser gain-of-function mutation were recently found to develop allergic dermatitis and spontaneous scratching (52). Since TRPV1 and TRPV3 are found in neurons and keratinocytes, modulation of these channels can potentially inhibit pruritus concurrently at the epidermis, by reducing mediators such as interleukins and nerve growth factor (NGF), and in the peripheral nerves (53). Moreover, certain agents, such as camphor, may act on both TRPV1 and TRPV3 (54), and a single agent can potentially be used to inhibit multiple receptors at different parts of the itch signaling pathway.

Cannabinoids have previously been shown to play a role in pruritus (55, 56) and creams containing *N*-palmitoylethanolamine (PEA) were reported to improve pruritus associated with AD (57), hemodialysis (58), prurigo nodularis and lichen simplex chronicus (59). The antipruritic effects of PEA may result from its inhibition of fatty-acid amide hydrolase (FAAH), the degrading enzyme of an endocannabinoid known as anandamide (60). Anandamide was found to reduce the activity of TRPV1 in primary sensory neurons (61) and may inhibit itch via this mechanism. In an acute allergenic mouse model, suppression of neuronal FAAH was shown to reduce the scratching response (62). Inhibiting FAAH and other enzymes that catabolize endogenous cannabinoids may thus be another strategy for the treatment of itch.

NGF is a neurotrophin that induces proliferation of nerve fibers (63) and upregulates neuropeptides such as substance P (64). Increased NGF and its receptor TrkA were found in AD lesions (65, 66), prurigo nodularis (67), pruritic psoriatic lesions (68) and pruritic contact dermatitis (69). Anti-NGF antibodies and TrkA inhibitors were shown to improve dermatitis and inhibit the proliferation of epidermal nerves in mice (70, 71), and anti-NGF antibodies have been used to treat pain in patients (72-74). Anti-NGF antibodies may possibly be a new strategy for the treatment of chronic pruritus.

Acetylcholine is a neurotransmitter that may have a role in mediating pruritus (75-77). Botulinum toxin, which inhibits the presynaptic release of acetylcholine, has been shown to reduce neurogenic inflammation (78-81) and was reported to improve notalgia paraesthetica, lichen simplex chronicus and neuropathic itch (82-84). However, it was also reported to be ineffective in other cases of neuropathic itch (85) and its potential as an antipruritic agent remains to be determined. In contrast to the usual subcutaneously administered form, topical botulinum toxin has recently been developed (86) and may be a promising test drug for localized pruritic diseases.

Mas-related G-protein coupled receptors (MRGPRX), a family of G protein-coupled receptors expressed exclusively in peripheral sensory neurons, were found to function as receptors in chloroquine-induced itch in mice (87). As MRGPRX receptors are activated by neuropeptides and the peripheral neurons expressing MRGPRX also express gastrin-releasing peptide (GRP), MRGPRX receptors may serve as a target for drugs to inhibit itch-signaling neurons.

Lysophosphatidic acid (LPA) was recently found to be a pruritogen in the sera of patients with cholestatic liver disease (88). The enzyme that synthesizes LPA, autotaxin, was also found to correlated with the degree of pruritus in the study. In systemic pruritic diseases, targeting pruritogens in the systemic circulation, such as LPA and autotaxin, can potentially be a new avenue in the development of itch therapeutics.

### Targeting the spinal cord

Various neuropeptides functioning in the synapses between primary and secondary neurons in the spinal cord may be potential central targets to inhibit central transmission of itch. Substance P and its receptor $NK_1$ have been shown to be important in mediating itch and neurogenic inflammation (89-92). Aprepitant, a tachykinin $NK_1$ receptor antagonist that has been used to prevent chemotherapy-induced emesis (93), was reported to be effective for chronic refractory pruritus in a case series (94). Controlled trials will be required to assess its antipruritic efficacy.

Another potential spinal target is GRP and its receptor, bombesin receptor $BB_2$ (also known as gastrin-releasing peptide receptor, GRP-R). In a recent mouse study, the expression of GRP and $BB_2$ was found to be restricted to a small group of dorsal root ganglia neurons and lamina I of the dorsal horn, respectively (95). Injection of a $BB_2$ receptor antagonist into the cerebrospinal fluid significantly inhibited scratching behavior induced by compound 40/80 (which degranulates mast cells to release histamine), a PAR2 receptor agonist, and chloroquine.

### Targeting the brain

Increasing evidence indicates that central sensitization develops in chronic pruritus (96, 97). This process is thought to occur in the spinal cord, similar to central sensitization in pain, which may result from defective descending inhibitory signals originating from various areas of the brainstem (98). The cerebral connections of these areas remain to be elucidated.

Positron emission tomography and functional magnetic resonance imaging used in recent years have identified multiple cerebral regions activated by itch, and these areas were diversely involved in sensory, motor and emotional functions. These regions were similar to regions activated by pain, with the exception of the precuneus, an area involved in episodic memory retrieval and which may be related to the affective aspects of itch (99, 100). Patients with AD were found to exhibit more activation of the anterior and posterior cingulate cortex and the dorsal lateral prefrontal cortex, and these findings may possibly represent a greater affective component during the processing of itch (99).

Sedating antihistamines, neuroleptics, antidepressants and opioids are drugs with central inhibitory effects that have been used in chronic pruritus. γ-Aminobutyric acid (GABA) and serotonin (5-HT)

were found to inhibit the cingulate cortex in mice, and this may possibly be a way whereby GABAergic drugs, namely gabapentin and pregabalin, and selective 5-HT reuptake inhibitor antidepressants work in pruritus (101). Improving brain imaging techniques has enabled the identification of cerebral areas activated by itch, and the use of drugs that act on these regions, in particular the anterior cingulate cortex, offers a new therapeutic approach in the management of chronic pruritus.

## TAILORED HOLISTIC APPROACH

The underlying causes of pruritus are diverse and the pathomechanisms of pruritus in various diseases differ. The treatment of pruritus should therefore be tailored to the disease process and should not be generalized. An example is the use of gabapentin, which was effective in pruritus associated with hemodialysis and lymphoma (102-104) but was shown to worsen pruritus of cholestasis (105). In addition, the treatment of pruritus should be individualized for each patient in accordance with the severity of pruritus, the effect on the quality of life, and the medical and social background.

In chronic pruritus, where there is prolonged input of itch signals from the skin and peripheral nerves, adaptive and sometimes aberrant changes occur in the spinal cord and brain. A comprehensive approach is required to address not only the skin pathology but also, concurrently, peripheral neuropathy (if present), central sensitization and the cognito-affective aspects. Treatment should be started early to avoid the development of central sensitization. Addressing abnormalities in the central processes is also of particular relevance in skin diseases in which pruritus is secondary to many varied peripheral processes, such as in AD. Attempts to inhibit the many different mediators and receptors with multiple agents will result in significant side effects; modulation of the central interpretation of itch signals using both pharmacological and nonpharmacological interventions will be a better approach.

A study demonstrated that 70% of 109 consecutive dermatology inpatients with chronic pruritus fulfilled the criteria for up to 6 psychiatric and psychosomatic diagnoses, and psychotherapeutic or psychiatric treatment was recommended for 62% of the patients (106). Chronic pruritus can sometimes be a manifestation of underlying psychiatric conditions, such as somatoform disorders and psychoses, and psychiatric evaluation is necessary in these cases. On the other hand, in most patients, there is an intricate relation between chronic itch and psychological factors. For example, background psychosocial stress may be the source or predisposing factor for some pruritic diseases, and the psychosocial morbidity resulting from chronic itch and scratching acts as a perpetuating factor, forming a vicious cycle. Interventions such as patient education (107), awareness training and habit reversal (108), relaxation and stress management (109), cognitive behavioral therapy (110), hypnosis (111, 112) and guided imagery (113) have been shown to improve the management of chronic pruritus. A multidisciplinary approach involving nurse education, psychological and/or psychiatric assessment and intervention, and social assistance would often be necessary to adequately address the psychodynamic issues and more effectively manage chronic pruritus.

## CONCLUSION

With a better understanding of the pathomechanism of itch processing, targeting the specific mediators and receptors and the neuronal pathways in each disease offers a new and promising approach to antipruritic treatment. Chronic pruritus is a multidimensional problem and requires a holistic management addressing the peripheral skin and neuronal pathologies, aberrant central processes and psychosocial factors early in the disease.

## DISCLOSURES

Dr. Yosipovitch is on the Advisory Board of GlaxoSmithKline and has served as a consultant for Regeneron, Johnson & Johnson and Unilever. Dr. Tey states no conflicts of interest.

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