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Pruritus: Management Algorithms and Experimental Therapies

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Abstract

Pruritus (itch) is a major symptom in many dermatologic as well as systemic diseases and has a dramatic impact on the quality of life in these patients. The symptom of itch has to be treated on the basis of its pathophysiology and its underlying disease. In daily practice, a "quick" diagnosis of the underlying disease is often difficult, although a rapid relief of the itch is desired. We often treat patients on the basis of the symptomatology. A rational therapeutic ladder for a symptomatic therapy is useful until the final diagnosis has been confirmed. There are probably many subtypes of pruritus, just as there are many diseases that cause itch. The pathophysiology in many subtypes of pruritus is still poorly understood, hindering a rapid and targeted treatment strategy. An extensive diagnostic workup is often required to determine the final cause(s) of the itch. Thus, in daily life, physicians often start with a more or less rational therapeutic strategy to combat the debilitating itch. We present possible therapeutic ladders that form the basis for effective therapeutic itch strategies in various diseases. On the basis of our current knowledge about the different pathophysiologies of itch, on clinical trials or case reports, and our own clinical experience, we aim to present therapeutic ladders for the rapid as well as long-term management of itch. Finally, we summarize current exciting developments of experimental strategies in itch research and in clinical development for itch therapy.

Important Aspects of Itch Treatment

Finding the Cause of the Itch

Establishing the correct diagnosis is key to the effective management of itch. A thorough history, with the physician identifying variations in the experienced symptoms, is crucial to understand the cause of the itch (Table 1). Next, the history and clinical appearance based on the classification[1] of the various itch subtypes will help to develop a diagnostic and therapeutic strategy for itch treatment.

Scratching Behavior

Various treatments can be used to combat the itch sensation. Interestingly, patients with atopic dermatitis (AD) scratch their skin until it bleeds to experience relief, whereas patients with urticaria prefer to rub. The difference lies in the fact that the superficial epidermal nerve fibers play a dominant role in AD whereas in urticaria, deeper dermal nerve fibers are affected that cannot be inactivated by an erosion. Cognitive therapy and the modification of

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behavior modification strategies (e. g., rubbing or cooling instead of scratching in AD patients; cutting the fingernails) will help to reduce skin lesions and ameliorate the vicious cycle of itching and scratching. Finally, cofactors such as infections, genetic diseases, or chronic venous insufficiency, for example, have to be considered.

Diagnostics

Itch can be caused by inflammatory skin diseases, exogenous trigger factors (e. g., mites, fungi, viruses, bacteria, toxins, allergens, haptens, ultraviolet [UV] radiation, wind or wool-fibers inducing alloknesis), endogenous trigger factors (e. g., systemic drugs, haptens, pH changes), or systemic diseases (e. g., chronic renal insufficiency, liver disease, tumors, HIV infection). To adequately treat a patient with pruritus, a significant effort must be focused on the history (Table 1), followed by a thorough physical examination and a complete diagnostic workup to determine the precise cause of the itch. The diagnostic workup should include complete red and white blood cell counts, including differential, sedimentation rate, C-reactive protein, creatinine and glucose levels, liver function tests (aspartate aminotransferase, alanine amino-transferase, alkaline phosphatase, total bilirubin), and thyroid function tests (thyroid-stimulating hormone, free T4). Second-level testing might include analysis of anemia (stool occult blood examination, iron, ferritin, transferrin, ESR, reticulocytes), immunoglobulin E, rapid plasma Reagin test for syphilis, HIV antibody test, and a chest radiograph and ultrasound of the abdomen.

More advanced specialized tests may be indicated by medical history and clinical appearance, for example, antinuclear antibody, hepatitis serology, antimitochondrial antibody, antigliadin antibody, antitransglutaminase antibody, parathyroid hormone, calcium, phosphate, immunoglobulin electrophoresis, functional anti-immunoglobulin E Fc-receptor antibody, serum tryptase, serotonin and its metabolites (urine), and stool for ova and parasites. Sometimes, allergy testing (prick or patch testing), histologic examination of affected skin, and direct immunofluorescence and radiologic imaging (magnetic resonance imaging, computed tomography) may also be beneficial. An age-appropriate malignancy workup is warranted if these initial studies are unremarkable or if the history and review of systems suggest a possible malignancy. Pruritus can precede a malignant process by years; therefore, regular monitoring (every six months) is recommended in these cases. In general, the approach to identify the origin of pruritus may be complete and multidisciplinary, for example, neurology, internal medicine, oncology, pharmacology, infectious disease, physical therapy and psychiatry.

Therapy of Pruritus

General Aspects

Many aspects of itch treatment for specific diseases are covered by other articles in this issue. Here, our focus is on a general therapeutic ladder to help determine initial and long-term treatment of patients who have the symptom of itch. Thus far, a general “itch therapeutic ladder” does not exist. Therefore, a rational combination of topical and systemic medications is given to patients with many different subtypes of itch. The selected therapy should be based on a thorough history (Table 1) and the underlying cause (Tables 2 and 3). Some general principles may be helpful in most cases (Tables 2–8).

Topical Therapies

Although not completely effective in most of the cases, topical therapy is an important part of a successful therapeutic intervention. Here, the best vehicle must be chosen (lotion or cream for acute phase, ointment for chronic phase and xerosis); alternatively, modern creams such as Cetaphil RESTORADERM (Galderma Canada Inc, Thornhill ON, Canada),

which have moisturizing epidermal properties of the epidermis, can be used for both acute and chronic pruritus. Patient compliance with consistent application should be monitored. The value of various topical anti-inflammatory or antipruritic agents has been recently discussed by others,[2–5] and in this issue (i. e., "Topical Therapies for Pruritus" by Elmariah and Lerner; "Management of Itch in Atopic Dermatitis" by Hong et al.; "Pruritus and Renal Failure" and "Pruritus in Elderly Patients-Eruptions of Senescence" by Berger and Steinhoff, all in this issue).

Systemic Therapies for Chronic Pruritus

Although various systemic therapies have been used to treat pruritus, no randomized controlled trials have shown one medication to be the most effective and safe. Most studies are case reports, case series, or open trials without long-term follow-up. Although recent basic research revealed the existence of certain histamine-independent itch pathways,[6,7] no unique itch biomarker or therapy is on the horizon for all subforms of pruritus.

Specific therapeutic regimens for itch caused by various diseases are described elsewhere in this issue ("Management of Itch in Atopic Dermatitis" by Hong et al; "Topical Therapies for Pruritus" by Elmirah and Lerner; "The Itch of Liver Disease" by Bergasa; "Cancer and Itch" by Chian et al; Oak-lander; and "Approach to Pruritus in the Adult HIV-Positive Patient" by Chua et al). Here, we focus on treatments that can be used by patients seen in daily practice who have moderate-to-severe chronic pruritus. In these cases, a therapeutic ladder is a promising approach to control pruritus (Tables 3–5).

Antihistamines/Mast Cell Stabilizers

Histamine is an autocasoid released by mast cells and basophils in many diseases. So far, four histamine receptors have been cloned (H1R, H2R, H3R, H4R) that activate not only peripheral pruriceptors but probably central histamine receptors also.[8] Recent studies indicate a role of H1R and H4R in certain subforms of itch (reviewed in Buddenkotte and Steinhoff[9]). So far, only H1R antagonists are available for treating pruritus and allergic diseases. H1R antagonists include sedative, first-generation antihistamines that tend to be sedating and have stronger anticholinergic effects. In principle, nonsedative (e. g., fexofenadine, 180 mg; loratadine, 10 mg) or poorly sedative (e. g., cetirizine, 10 mg) H1R antagonists can be tried in certain subforms of itch (Tables 3 and 4). Nonsedative H1R antagonists are recommended in most forms of urticaria.[10,11] Often greater doses (three to four times greater than recommended antiallergic doses) become effective as an antipruritic regimen. Of note, H1R blockers are competitive antagonists and thus may be ineffective when higher levels of histamine are released. If low-dose as well as high-dose antihistamines fail, non-antihistamines agents are necessary (Table 5). For the treatment of AD, a specific modified regimen is recommended (Tables 2, 6, and 7). In general, high-dose antihistamine (AH) regimens are well tolerated. Side effects (antimuscarinergic effects, sedation, antimotion effects) and contraindications have to be considered, especially in elderly patients, because of potential arrythmias or renal dysfunction attributable to some AH (reviewed in Church et al[12]).

Except for urticaria, the efficacy of systemic AH in pruritic diseases has been poorly documented in randomized, double-blind, placebo-controlled clinical trials (reviewed in Thurmond et al[13]). Doxepin 10–100 mg d^{-1} has been a widely used strategy to combat various subforms of pruritus. It has antihistaminergic, antiserotoninergic, and antiadrenergic effects and is a relatively safe drug with a long history of use. Gradual dose escalation (e. g., starting at 10 mg and adding 10 mg every third night) is important. In 19 clinical trials between 1950 and 2009, topical doxepin was the only AH that showed efficacy for the treatment of chronic pruritus. Thus, topical doxepin may be an alternative to systemic

treatment with less sedation; however, doxepin not infrequently causes allergic contact dermatitis.[14]

In general, we prefer an "add-on" approach instead of a replacement strategy, i. e., a nonsedative AH in the morning (eg, fexofenadine or loratadine), a nonsedative or mildly sedative AH in the afternoon (e. g., azelastine, cetirizine), and a mildly sedative or sedative AH in the evening/at night (first-generation AH), if there are no contraindications (e. g., renal disease, age, risk of arrhythmia). AHs that work on different antiinflammatory pathways (e. g., blocking neuropeptide release, blocking leukotrienes) are preferable.[15] Only a few reports have demonstrated an effect of mast-cell stabilizers like ketotifen[16–18] in itch. In our experience, ketotifen is rarely effective, except in certain subtypes of urticaria.

Systemic Glucocorticosteroids

Systemic glucocorticosteroids (SGCs) exert their effects by activating cytoplasmic GC receptors (GCR), thereby building a GC/GCR complex that acts as a transcription factor. They modulate cytokines, chemokines, and lipid mediators (PLA2, prostanoids, and leukotrienes), as well as nitric oxide and signal transduction pathways, such as nuclear factor-κB. SGCs decrease edema, leukocyte migration and phagocytosis and are effective in many pruritic diseases, such as AD, psoriasis, urticaria, lupus erythematoses, bullous pemphigoid, lichen planus, cutaneous T-cell lymphoma, and some causes of drug-induced pruritus.

The kinetics of the antipruritic effect of SGCs matches the antiinflammatory action of SGC, indicating that cytokines (e. g., interleukin [IL]-6, IL-31), chemokines, and lipid mediators (e. g., PGE_2) may be also involved in pruritus. This is supported by the example of IL-31, which is ultimately involved in the pathophysiology of AD. Despite the murine in vivo data, evidence showing a direct connection between immune cells and neuronal cells is still lacking. IL-2 and interferon gamma in general do not cause itch. Thus, the cellular mechanisms by which SGCs suppress itch in different pruritic diseases are still unclear and probably broad.

The use of SGC should be limited to controlling acute, severe forms of pruritus. Undesired side effects (e. g., ACTH suppression, iatrogenic Cushing syndrome, hyperglycemia, osteoporosis, gastric ulcer, hypertension, infections, impaired wound healing, glaucoma, mental dysfunction), as well as rebound effect have to be considered in each patient individually. SGCs should be used at sufficient dosages (starting at 0.5–2 mg/kg body weight, depending on underlying disease), and then tapered down quickly while starting an alternative or additional steroid-sparing therapy based on the origin of the pruritus. For patients with AD, SGCs are not necessary.

Other Immunosuppressants

Systemic steroids and cyclosporine A are the immunosuppressants that have been studied most widely in different subforms of pruritus. Studies in animals indicate that both tacrolimus and cyclosporine A may be better as antipruritic agents than SGC.[19] Cyclosporine A has been shown to be effective for the treatment of itch in AD and certain autoimmune diseases. Successful treatment of prurigo nodularis of different origin has been described in 16 patients with an efficacy of 92% and a side effect profile of 50%.[20] Cyclosporine A may be also effective in other pruritic diseases that have a dominant T cell infiltrate, like lichen planus or drug-induced pruritus. Adjusted for renal function, cyclosporine A can be started at 3–5 mg/kg body weight, and later reduced to 3 mg/kg.

The benefit of other systemic immunosuppressants, such as-cyclophosphamide, tacrolimus, mycophenolate mofetil, and azathioprine, as antipruritic agents is poorly documented. There have been no placebo-controlled, randomized trials. One case report described successful treatment of retractable lichen amyloidosus with dexamethasone/cyclophosphamide therapy.[21] Case series reports indicated a beneficial effect of mycophenolate mofetil as an antiinflammatory/antipruritic drug for chronic eczemas and AD,[21,22] but neither series had a control group. Azathioprine can be useful for photodermatitis-associated pruritus. It was also used successfully in adults or children with severe AD, although liver-associated side effects were observed.[23] However, azathioprine can also induce pruritic hepatitis.[24,25] Finally, methotrexate decreased itch significantly in patients with primary biliary cirrhosis.[26] When any of these drugs are used for refractory itch, side effect profiles have to be considered thoroughly. Additional controlled safety and tolerability studies are necessary to evaluate the impact of these drugs in certain subforms of severe pruritus.

Thalidomide

Thalidomide is approved for treatment of erythema nodosum leprosum and multiple myeloma, and is occasionally used off-label for various refractory dermatologic diseases, including pruritus. Off-label uses include prurigo nodularis, actinic prurigo, lichen planus, graft-versus-host disease, renal itch, and scleroderma. Thalidomide is used in doses between 25 and 400 mg/d in pruritic diseases. A beneficial effect of thalidomide (200 mg/d) was reported in a patient with severe pruritic Hodgkin lymphoma.[27] Successful therapy of prurigo nodularis has also been described at a low dose of 100 mg/d[28] or less.

Opioid-Receptor Antagonists and Agonists

The human body can produce endogenous opioids, such as endorphins, enkephalins and dynorphins. Opioids are important transmitters in the pain pathways that perform by activating opioid receptors (mu, kappa, delta). Although activation of muopioid receptors results in pruritus, activation of kappa opioid receptors suppresses itch at the spinal cord level (Cevikbas et al[8] and references therein).

In contrast to many other drugs used as antipruritic agents, the efficacy of muopioid receptor antagonists like nalmefene, naloxone (intravenously) or naltrexone (orally) is well documented in randomized and other controlled clinical trials.[29–37] Because of its side effects, including drowsiness, dizziness, sedation, and gastrointestinal disturbances, the dose of naltrexone should be gradually increased (starting at 25 mg, adding 25 mg every third day until 100 mg). The kappa-opioid receptor agonist TRK-820 (nalfurafine) is approved for the treatment of renal itch.[38 – 40] Current trials are investigating the effectiveness of nalfurafine in atopic dermatitis.

Antipruritc Antidepressants

Selective Serotonin-Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) exert their effects by blocking the reuptake of serotonin into presynaptic vesicles, thereby significantly increasing the concentration of serotonin in the spinal cord and brain. Although not completely understood, the antipruritic role of centrally released serotonin is documented by various case reports, case series and controlled trials. SSRIs have been used to treat pruritus in patients with prurigo, AD, psychogenic pruritus, paraneo-plastic pruritus, and polycythemia vera, for example. Effectiveness has been documented with paroxetine, 20 mg d^{-1}, fluvoxamine, and sertraline.[41–45]

Sertraline, 75–100 mg d^{-1} has been successfully used in cholestatic pruritus.[46] A combination of sertraline and gaba-pentin was successfully used in patients with cutaneous T-cell lymphoma (CTCL).[46] In a 2-arm study, 40 of 72 patients with chronic pruritus experienced a good or very good effect when treated with either oral paroxetine or fluvoxamine.[45] Side effects to be considered are insomnia, weight loss, appetite loss, and sexual dysfunction (see Tables 6 and 7).

Serotonin-Norepinephrine Reuptake Inhibitors

Serotonin-norepinephrine reuptake inhibitors (SNRIs) were developed later than SSRIs, but their capacity as an antipruritic as compared with SSRIs is unclear. The most common SNRI used as an antidepressant and with experience as an antipruritic is venlaxafine (i. e., Effexor; Pfizer, New York, NY). Venlaxafine has been used at doses between 150 and 300 mg/d. At low doses (150 mg/d), venlaxafine works mainly as an SSRI, whereas at moderate doses (150–300 mg/d), it acts as an SNRI. At doses above 300 mg, it can also inhibit the dopamine transporter, thereby enhancing dopa-mine, concentrations.

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) were originally designed from antihistamines in the 1950s. Chlorpromazine was the prototype, which also explains the overlapping side effect profiles. TCAs mainly act at the serotoninergic and/or noradrenergic receptor level on postsynaptic neurons (reviewed by Cevikbas et al[8]).

TCAs primarily act as selective SNRIs by blocking the serotonin transporter and the norepinephrine transporter. This results in increased concentrations of serotonin and/or norepinephrine. The mechanism by which these transmitters affect itch sensation is not known, but one mechanism may be via central opioid modulation.

Differences among TCAs derive from the fact that some also affect serotonin receptors, *N*-Methyl-D-aspartate receptors, adrenergic receptors, histamine receptors, Ca-channels, or sodium channels, with different affinity and selectivity. This explains the variety of side effects of TCAs.

Doxepin is a TCA that has simultaneous marked antihistaminergic (sedative) as well as antimuscarinergic effects (see the section “Antihistamines/Mast Cell Stabilizers”). Doxepin (10–100 mg oral) acts on serotonin-, histamine-, and noradrenergic receptors. In our experience, low-dose doxepin is also useful in patients with renal itch, atopic dermatitis and various pruritic non-inflammatory dermatoses or HIV-induced pruritus.[47,48] Unfortunately, its effectiveness is rather unpredictable. Patients start with 10 mg of doxepin at night, which is up-dosed every third day until the level of sedation is no longer tolerable. Because of their sedative and antimuscarinergic effects, TCAs should be considered as second or third-line therapy. No large controlled studies have compared the effects of TCAs, tetracyclic antidepressants (TTCAs), SSRIs or SNRIs with respect to efficacy, safety and tolerability (see Tables 6 and 7).

TTCAs

Similarly to TCAs, TTCAs act upon serotonin-, norepinephrine, and dopamine release, as well as on adrenergic, muscarinergic, and histamine receptors, but with different affinities and with a different predominance of side effects. Mirtazepine mainly acts as a serotonin- and dopamine-reuptake inhibitor. We find mirtazepine at doses between 15 and 30 mg/d beneficial for chronic pruritus of different causes.[49] Mirtazepine is helpful as a prophylaxis of morphine-induced pruritus;[50] however, some patients complain that in addition to the effects of TCA they experience weight gain and generalized edema. Many TTCAs have not

been tested for use as anipruritics, although their pharmacologic profiles differ from one another (Table 6).

Serotonin-Receptor Antagonists

Serotonin-receptor antagonists (SRAs) act as inhibitors of the serotonin receptor subtype (5-HT3) pathway, a strategy that is contradictory to that of SSRIs, TCIs, and TTCIs. Examples are ondansetron, 8–24 mg d^{-1}, tropisetron, 5 mg d^{-1}, or granisetron, 1 mg d^{-1}.[51,58] Data reporting that blocking the 5-HT3 receptor pathway is of benefit for suppressing itch are poor and contradictory.[51,59 – 67] Current published studies provide a very poor rationale for the usage of SRAs, which may be attributable to the limited success in morphine-induced itch, probably by interfering with muopioid receptors on the spinal cord level.

Antipruritic Anticonvulsants (APACs)

Gabapentin

Anticonvulsants include neuronally active substances, such as carbamazepine, valproic acid, gabapentin, and pregabalin. Anticonvulsants that have been tested for their ability to suppress itch are gabapentin and its prodrug, pregabalin (Table 6). Both are known for their ability to inhibit neuropathic pain.[68,69] The first description at the beneficial effect of gabapentin for the treatment of brachioradial pruritus was in 1999.[70] The potential antipruritic effect of APACs is probably based on their ability to modulate calcium channels, inhibit glutamate synthesis and release, and/or inhibit GABA-ergic pathways in the central nervous system.[69,71] An additional peripheral effect of APACs on peripheral nerves has recently been described.[72] Case reports, case series reports, and a placebo-controlled double-blinded study indicate a role of gabapentin against prurigo, brachioradial pruritus, notalgia paresthetica, senile pruritus, postburn itch, morphine-induced itch, CTCL, as well as idiopathic, liver-associated and renal itch.[73–81]

Dosages vary between 900 and 3600 mg of gabapentin daily (Table 6).[70,71,73,78,82,83] The side effect profile of gabapentin includes back pain, blurred vision, constipation, diarrhea, drowsiness, dry mouth, nausea, stomach upset, tired-ness, vomiting, and weight gain. Contraindications are allergies and risk of seizures. Gabapentin and SSRIs are reportedly successful for treating prurigo nodularis.[83,84] Gabapentin was not better than placebo in a recent study of variable doses (maximum 2400 mg daily) in patients who had various subforms of liver-associated itch, although the two groups were not matched for age and gender.[46] Thus, placebo-controlled, double-blind cross-over studies with age- and gender-matched groups of patients are needed to clarify the effectiveness of gabapentin in various subforms of chronic pruritus.

Pregabalin

On the basis of its pharmacologic profile, the prodrug of gabapentin, pregabalin, works by the same mechanism as gabapentin. In case reports, pregabalin has been shown to be effective against aquagenic and neuropathic itch of various origin.[45] Side effects of pregabalin, especially dizziness, are often observed with dosage increase. As with gabapentin, placebo-controlled, double-blind cross-over studies with age- and gender-matched patient groups and similar subforms of pruritus would clarify the effectiveness of APACs against chronic pruritus.

Phototherapies

The effectiveness of UV therapy (UVA, UVA1, broad-band UVB, narrow-band UVB, psoralen UV [PUVA]) is well documented for the treatment of chronic pruritus of different

origin. Its immunomodulatory effects make phototherapy especially useful for treating inflammatory dermatoses, but also CTCL, solar urticaria (hardening), or systemic diseases (cancer-associated itch, renal itch, liver-associated itch). These effects are mainly caused by the inhibition of proinflammatory mediators, such as IL-1 and tumor necrosis factor-lapha, or release of anti-inflammatory neuropeptides. A direct role of phototherapy on the release of other antipruritic mediators from cutaneous cells is currently unknown.[85]

UV radiation exerts an immunosuppressive and anti-inflammatory effect in various pruritic inflammatory skin diseases, including AD, or by modulating proliferation and apoptosis in neoplasms like CTCL. A direct impact of UV light on sensory nerves during neoplastic processes is still under debate. Thus, whether UV radiation may have a direct beneficial effect on sensory nerves by controlling neuronal function is not known.

A beneficial role of phototherapy has been demonstrated in atopic dermatitis (See "Management of Itch in Atopic Dermatitis" by Hong et al in this issue),[3] prurigo nodularis (UVA1, narrow band UVB and PUVA),[86 – 88] solar urticaria,[89] aquagenic pruritus,[90] CTCL,[91] Hodgkin lym-phoma,[92] polycythemia vera (narrow-band UVB),[93] HIV infection,[94] and folliculitis of pregnancy.[95] Combinations of narrow-band UVB with steroids/antihistamines or cyclo-sporin A have been successfully used for the treatment of AD or lichen amyloidosus.[96,97] Of note, phototherapy is a valuable alternative for histamine- or steroid-resistant pruritus during pregnancy. PUVA in particular is useful for the treatment of CTCL. UV radiation also ameliorates pruritus in renal disease-associated itch.[98–101] Although not completely comparable, the combination of UVA and UVB appears to be better than UVA[102] or UVB311 phototherapy[103,104] in renal pruritus.

Leukotriene Receptor Antagonists

The value of leukotriene-receptor antagonists (LRAs), as compared with that of other anti-inflammatory or anti-allergic drugs, is not clear, both in human disease and mouse models. Only a few controlled trials have explored a direct role of LRAs as antipruritics, and the results are contradictory.[105–110] So far, a beneficial effect of LRAs on pruritus has been only described in combination with non-sedative antihistamines in patients with urticaria.[108,111,112]

Adjuvant Therapies: Acupuncture, Hypnosis, Psychosomatic Therapy, and Cognitive Therapy

Adjuvant behavioral, cognitive, or psychological therapies have a role in treatment of itch, but a discussion is beyond the scope of this review. We refer the reader to other recent reviews[1] or publications[113–119] about this topic.

Experimental Therapies

The spectrum of therapeutic strategies for chronic pruritus has recently emerged. Biotechnological advances, such as the ability of generating humanized molecules that target specific cellular structures has made it possible to develop novel agents, such as the IL-4 and IL-4 receptor antagonists. Other monoclonal antibody ("biologics"), such as anti-IL-31 or antinerve growth factor, are being developed.

Novel oral treatments, such as the NK1 receptor-antagonist aprepitant (emend) have just now been reported to be effective in various subforms of itch. Larger, better controlled, randomized studies have shown the efficacy of anti-inflammatory drugs like cyclosporine A as antipruritics. Other modern oral drugs like the kappa-opioid receptor agonist nalfurafine

target pruritic pathways directly, making it possible to imagine better systemic or topical muopioid receptor antagonists as a future strategy.

Other future targets will be gastrin-releasing peptide and its receptor, which act on the level of the spinal cord and integrate many histamine- and histamine-independent itch pathways. Another histamine itch pathway is the protease pathway via activation of G protein-coupled protease-activated receptors. Several strategies are possible, either by targeting the proteases or the receptor, or modulating the effects of protease inhibitors (eg, LEKTI 1).

Capsaicin is the prototype of topical antipruritic agents that targets the transient receptor potential (TRP) gene family of ion channels that respond to physical activation (heat, cold), protons (pH changes) or biological mediators (eg, prostanoids) and counteract itch via activating pain neurons. Advanced, more selective topical, as well as systemic, strategies are conceivable that target TRPV1, TRPV3, or -4.

Cannabinoid receptor agonists have been demonstrated as effective topical modalities for itch treatment, although their potency in activating receptors can be certainly improved. Further topical or systemic strategies using cannabinoid receptors as targets are promising for itch therapy.

The fact that itch affects the skin, immune system, and the peripheral and central nervous system means that complex and combinatory pathways may be more effective than a single-line approach. Combinations of the new systemic drugs with novel topical agents are feasible, for example, combining systemic antipruritic drugs like NK1R antagonists or anti-IL-4, with effective topical anti-inflammatory agents like tacrolimus, pimecrolimus, or newer corticosteroids.

The discovery of antipruritic antidepressants has opened new avenues for manipulating neurotransmitter-modulating anti-itch pathways. Here, understanding the various crucial neurotransmitters in the skin, neurons, spinal cord neurons, and central nervous system is still in its infancy. The efficacy of advanced topical antipruritic antidepressants, neuroleptics (eg, gabapentin) or cannabinoids still needs to be demonstrated. Considering our increased understanding about the pathophysiology of pruritus, and the relationship of nerves and the immune system, we predict improved therapeutic capabilities for the treatment of chronic pruritus in the future.

Conclusion and Future Directions

In this review, we described the usefulness of the available medications against chronic pruritus of different origin, and provided a systematic therapeutic ladder for daily usage in a dermatologic or general medical practice. Clearly, the number of topical and systemic drugs used for the different subforms of pruritus is increasing, but optimal therapy is hampered by the fact that our understanding of crucial itch mediators and receptors in the various subforms of itch is poor. Therefore, we often do not know which medication to apply for specific subtypes of itch and why. Most studies of medications used for itch are case reports, case series reports, or contradictory placebo-controlled clinical trials. Therefore, well-designed placebo-controlled, randomized trials are needed to verify the effectiveness of many antipruritic agents currently being used.

References

1. Suárez AL, Feramisco JD, Koo J, et al. Psychoneuroimmunology of psychological stress and atopic dermatitis: Pathophysiologic and therapeutic updates. Acta Derm Venereol. in press.
2. Lynde CB, Kraft JN, Lynde CW. Novel agents for intractable itch. Skin Ther Lett. 2008; 13:6–9.

3. 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. [PubMed: 19732254]
4. Curtis AR, Tegeler C, Burdette J, et al. Holistic approach to treatment of intractable central neuropathic itch. J Am Acad Dermatol. 2011; 64:955. [PubMed: 21292347]
5. Patel T, Yosipovitch G. Therapy of pruritus. Exp Opin Pharmacother. 2010; 11:1673–1682.
6. Sun YG, Chen ZF. A gastrin-releasing peptide receptor mediates the itch sensation in the spinal cord. Nature. 2007; 448:700–703. [PubMed: 17653196]
7. Steinhoff M, Neisius U, Ikoma A, et al. Proteinase-activated receptor-2 mediates itch: A novel pathway for pruritus in human skin. J Neurosci. 2003; 23:6176–6180. [PubMed: 12867500]
8. Cevikbas F, Steinhoff M, Ikoma A. Role of spinal neurotransmitter receptors in itch: new insights into therapies and drug development. CNS Neurosci Ther CNS Neurosci Ther. 2010 Oct 15. [Epub ahead of print]. 10.1111/j.1755-5949.2010.00201.x
9. Buddenkotte J, Steinhoff M. Pathophysiology and therapy of pruritus in allergic and atopic diseases. Allergy. 2010; 65:805–821. [PubMed: 20384615]
10. Zuberbier T, Bindslev-Jensen C, Canonica W, et al. EAACI/GA2LEN/EDF guideline: Management of urticaria. Allergy. 2006; 61:321–331. [PubMed: 16436141]
11. Schulz S, Metz M, Siepmann D, et al. Antipruritic efficacy of a high-dosage antihistamine therapy. Results of a retrospectively analysed case series [in German]. Hautarzt. 2009; 60:564–568. [PubMed: 19430742]
12. Church MK, Maurer M, Simons FE, et al. Risk of first-generation H(1)-antihistamines: A G(2)LEN position paper. Allergy. 2010; 65:459–466. [PubMed: 20146728]
13. 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. [PubMed: 18172439]
14. Eschler DC, Klein PA. An evidence-based review of the efficacy of topical antihistamines in the relief of pruritus. J Drugs Dermatol. 2010; 9:992–997. [PubMed: 20684150]
15. Buddenkotte, J.; Maurer, M.; Steinhoff, M. Role of histamine and antihistamines in atopic dermatitis and pruritus. In: Thurmond, R., editor. Histamine in Inflammation. Philadelphia: Springer/Landes Bioscience; 2010. p. 73-80.
16. Francos GC, Kauh YC, Gittlen SD, et al. Elevated plasma histamine in chronic uremia. Effects of ketotifen on pruritus. Int J Dermatol. 1991; 30:884–889. [PubMed: 1816135]
17. Dimković N, Djukanović L, Radmilović A, et al. Uremic pruritus and skin mast cells. Nephron. 1992; 61:5–9. [PubMed: 1528340]
18. Riccardi VM. A controlled multiphase trial of ketotifen to minimize neurofibroma-associated pain and itching. Arch Dermatol. 1993; 129:577–581. [PubMed: 8481017]
19. Yamashita H, Ito T, Kato H, et al. Comparison of the efficacy of tacrolimus and cyclosporine A in a murine model of dinitrofluorobenzene-induced atopic dermatitis. Eur J Pharmacol. 2010; 645:171–176. [PubMed: 20674565]
20. Siepmann D, Luger TA, Ständer S. Antipruritic effect of cyclosporine microemulsion in prurigo nodularis: Results of a case series. J Dtsch Dermatol Ges. 2008; 6:941–946. [PubMed: 18445069]
21. Gupta R, Gupta S. Dexamethasone cyclophosphamide pulse therapy in lichen amyloidosus: A case report. J Dermatol Treat. 2007; 18:249–251.
22. Jackson JM, Fowler JF Jr, Callen JP, et al. Mycophenolate mofetil for the treatment of chronic dermatitis: An open-label study of 16 patients. J Drugs Dermatol. 2010; 9:356–362. [PubMed: 20514793]
23. Hon KL, Ching GK, Leung TF, et al. Efficacy and tolerability at 3 and 6 months following use of azathioprine for recalcitrant atopic dermatitis in children and young adults. J Dermatol Treat. 2009; 20:141–145.
24. Appelman M, Wintzen M. Pruritus and leucocytoclastic vasculitis due to azathioprine. Dermatology (Basel). 2005; 210:366. [PubMed: 15942233]

25. Ben Salem C, Ben Salah L, Belajouza C, et al. Azathioprine-induced severe cholestatic hepatitis in patient carrying TPMT*3C polymorphism. Pharm World Sci. 2010; 32:701–703. [PubMed: 20972624]
26. Giljaca V, Poropat G, Stimac D, et al. Methotrexate for primary biliary cirrhosis. Cochrane Database Syst Rev. 2010:CD:004385. [PubMed: 20464729]
27. Gonçalves F. Thalidomide for the control of severe paraneoplastic pruritus associated with Hodgkin's disease. Am J Hosp Palliat Care. 2010; 27:486–487. [PubMed: 20231735]
28. Orlando A, Renna S, Cottone M. Prurigo nodularis of Hyde treated with low-dose thalidomide. Eur Rev Med Pharmacol Sci. 2009; 13:141–145. [PubMed: 19499850]
29. Bernstein JE, Swift R. Relief of intractable pruritus with naloxone. Arch Dermatol. 1979; 115:1366–1367. [PubMed: 389168]
30. Wolfhagen FH, Sternieri E, Hop WC, et al. Oral naltrexone treatment for cholestatic pruritus: A double-blind, placebo-controlled study. Gastroenterology. 1997; 113:1264–1269. [PubMed: 9322521]
31. Brune A, Metze D, Luger TA, et al. Antipruritic therapy with the oral opioid receptor antagonist naltrexone. Open, non-placebo controlled administration in 133 patients. Hautarzt. 2004; 55:1130–1136. [PubMed: 15517116]
32. Bergasa NV, Schmitt JM, Talbot TL, et al. Open-label trial of oral nalmefene therapy for the pruritus of cholestasis. Hepatology. 1998; 27:679–684. [PubMed: 9500694]
33. Stander, S.; Metze, D. Treatment of pruritus in internal and dermatological diseases with opioid receptor antagonists. In: Yosipovitch, G., et al., editors. Itch: Basic Mechanisms and Therapy. New York: Marcel Dekker; 2004. p. 259-277.
34. Bergasa NV, Alling DW, Talbot TL, et al. Oral nalmefene therapy reduces scratching activity due to the pruritus of cholestasis: A controlled study. J Am Acad Dermatol. 1999; 41:431–434. [PubMed: 10459118]
35. Pauli-Magnus C, Mikus G, Alscher DM, et al. Naltrexone does not relieve uremic pruritus: Results of a randomized, double-blind, placebo-controlled crossover study. J Am Soc Nephrol. 2000; 11:514–519. [PubMed: 10703675]
36. Peer G, Kivity S, Agami O, et al. Randomised crossover trial of naltrexone in uraemic pruritus. Lancet. 1996; 348:1552–1554. [PubMed: 8950882]
37. Terg R, Coronel E, Sordá J, et al. Efficacy and safety of oral naltrexone treatment for pruritus of cholestasis, a crossover, double blind, placebo-controlled study. J Hepatol. 2002; 37:717–722. [PubMed: 12445410]
38. Togashi Y, Umeuchi H, Okano K, et al. Antipruritic activity of the kappa-opioid receptor agonist, TRK-820. Eur J Pharmacol. 2002; 435:259–264. [PubMed: 11821035]
39. Umeuchi H, Togashi Y, Honda T, et al. Involvement of central muopioid system in the scratching behavior in mice, and the suppression of it by the activation of kappa-opioid system. Eur J Pharmacol. 2003; 477:29–35. [PubMed: 14512095]
40. Wikström B, Gellert R, Ladefoged SD, et al. Kappa-opioid system in uremic pruritus: Multicenter, randomized, double-blind, placebo-controlled clinical studies. J Am Soc Nephrol. 2005; 16:3742–3747. [PubMed: 16251241]
41. Tefferi A, Fonseca R. Selective serotonin reuptake inhibitors are effective in the treatment of polycythemia vera-associated pruritus. Blood. 2002; 99:2627. [PubMed: 11926187]
42. Zylicz Z, Smits C, Krajnik M. Paroxetine for pruritus in advanced cancer. J Pain Symptom Manage. 1998; 16:121–124. [PubMed: 9737103]
43. Biondi M, Arcangeli T, Petrucci RM. Paroxetine in a case of psychogenic pruritus and neurotic excoriations. Psychother Psychosom. 2000; 69:165–166. [PubMed: 10773782]
44. 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. [PubMed: 14654262]
45. Ständer S, Böckenholt B, Schürmeyer-Horst F, et al. Treatment of chronic pruritus with the selective serotonin re-uptake inhibitors paroxetine and fluvoxamine: Results of an open-labelled, two-arm proof-of-concept study. Acta Derm Venereol. 2009; 89:45–51. [PubMed: 19197541]

46. Mayo MJ, Handem I, Saldana S, et al. Sertraline as a first-line treatment for cholestatic pruritus. Hepatology. 2007; 45:666–674. [PubMed: 17326161]
47. Smith PF, Corelli RL. Doxepin in the management of pruritus associated with allergic cutaneous reactions. Ann Pharmacother. 1997; 31:633–635. [PubMed: 9161661]
48. Smith KJ, Skelton HG, Yeager J, et al. Pruritus in HIV-1 disease: Therapy with drugs which may modulate the pattern of immune dysregulation. Dermatology (Basel). 1997; 195:353–358. [PubMed: 9529556]
49. Davis MP, Frandsen JL, Walsh D, et al. Mirtazapine for pruritus. J Pain Symptom Manage. 2003; 25:288–291. [PubMed: 12614964]
50. Sheen MJ, Ho ST, Lee CH, et al. Prophylactic mirtazapine reduces intrathecal morphine-induced pruritus. Br J Anaesth. 2008; 101:711–715. [PubMed: 18713761]
51. Weisshaar E, Dunker N, Röhl FW, et al. Antipruritic effects of two different 5-HT3 receptor antagonists and an antihistamine in haemo-dialysis patients. Exp Dermatol. 2004; 13:298–304. [PubMed: 15140020]
52. Schwörer H, Ramadori G. Treatment of pruritus: A new indication for serotonin type 3 receptor antagonists. Clin Invest. 1993; 71:659–662.
53. Jones EA. Relief from profound fatigue associated with chronic liver disease by long-term ondansetron therapy. Lancet. 1999; 354:397. [PubMed: 10437877]
54. Schwörer H, Ramadori G. Improvement of cholestatic pruritus by ondansetron. Lancet. 1993; 341:1277. [PubMed: 8098410]
55. Raderer M, Müller C, Scheithauer W. Ondansetron for pruritus due to cholestasis. N Engl J Med. 1994; 330:1540. [PubMed: 8164723]
56. Andrews PA, Quan V, Ogg CS. Ondansetron for symptomatic relief in terminal uraemia. Nephrol Dial Transplant. 1995; 10:140. [PubMed: 7724017]
57. Schwörer H, Hartmann H, Ramadori G. Relief of cholestatic pruritus by a novel class of drugs: 5-hydroxytryptamine type 3 (5-HT3) receptor antagonists: Effectiveness of ondansetron. Pain. 1995; 61:33–37. [PubMed: 7644246]
58. Albares MP, Betlloch I, Guijarro J, et al. Severe pruritus in a haemo-dialysed patient: Dramatic improvement with granisetron. Br J Dermatol. 2003; 148:376–377. [PubMed: 12588407]
59. O'Donohue JW, Pereira SP, Ashdown AC, et al. A controlled trial of ondansetron in the pruritus of cholestasis. Aliment Pharmacol Ther. 2005; 21:1041–1045. [PubMed: 15813840]
60. Ashmore SD, Jones CH, Newstead CG, et al. Ondansetron therapy for uremic pruritus in hemodialysis patients. Am J Kidney Dis. 2000; 35:827–831. [PubMed: 10793015]
61. Borgeat A, Stirnemann HR. Ondansetron is effective to treat spinal or epidural morphine-induced pruritus. Anesthesiology. 1999; 90:432–436. [PubMed: 9952149]
62. Kjellberg F, Tramèr MR. Pharmacological control of opioid-induced pruritus: A quantitative systematic review of randomized trials. Eur J Anaesthesiol. 2001; 18:346–357. [PubMed: 11412287]
63. Müller C, Pongratz S, Pidlich J, et al. Treatment of pruritus in chronic liver disease with the 5-hydroxytryptamine receptor type 3 antagonist ondansetron: A randomized, placebo-controlled, double-blind crossover trial. Eur J Gastroenterol Hepatol. 1998; 10:865–870. [PubMed: 9831410]
64. Layegh P, Mojahedi MJ, Malekshah PE, et al. Effect of oral granisetron in uremic pruritus. Indian J Dermatol Venereol Leprol. 2007; 73:231–234. [PubMed: 17675729]
65. Zenker S, Schuh T, Degitz K. Therapy of pruritus associated with skin diseases with the serotonin receptor antagonist ondansetron [in German]. J Dtsch Dermatol Ges. 2003; 1:705–710. [PubMed: 16285277]
66. Balaskas EV, Bamihas GI, Karamouzis M, et al. Histamine and serotonin in uremic pruritus: Effect of ondansetron in CAPD-pruritic patients. Nephron. 1998; 78:395–402. [PubMed: 9578065]
67. Larijani GE, Goldberg ME, Rogers KH. Treatment of opioid-induced pruritus with ondansetron: Report of four patients. Pharmacotherapy. 1996; 16:958–960. [PubMed: 8888093]
68. Backonja M, Glanzman RL. Gabapentin dosing for neuropathic pain: Evidence from randomized, placebo-controlled clinical trials. Clin Ther. 2003; 25:81–104. [PubMed: 12637113]

69. Scheinfeld N. The role of gabapentin in treating diseases with cutaneous manifestations and pain. Int J Dermatol. 2003; 42:491–495. [PubMed: 12786883]
70. Bueller HA, Bernhard JD, Dubroff LM. Gabapentin treatment for brachioradial pruritus. J Eur Acad Dermatol Venereol. 1999; 13:227–228. [PubMed: 10642063]
71. Winhoven SM, Coulson IH, Bottomley WW. Brachioradial pruritus: Response to treatment with gabapentin. Br J Dermatol. 2004; 150:786–787. [PubMed: 15099389]
72. Yang RH, Wang WT, Chen JY, et al. Gabapentin selectively reduces persistent sodium current in injured type-A dorsal root ganglion neurons. Pain. 2009; 143:48–55. [PubMed: 19269740]
73. Gunal AI, Ozalp G, Yoldas TK, et al. Gabapentin therapy for pruritus in haemodialysis patients: A randomized, placebo-controlled, double-blind trial. Nephrol Dial Transplant. 2004; 19:3137–3139. [PubMed: 15575002]
74. Yesudian PD, Wilson NJ. Efficacy of gabapentin in the management of pruritus of unknown origin. Arch Dermatol. 2005; 141:1507–1509. [PubMed: 16365250]
75. Schneider JC, Harris NL, El Shami A, et al. A descriptive review of neuropathic-like pain after burn injury. J Burn Care Res. 2006; 27:524–528. [PubMed: 16819359]
76. Demierre MF, Taverna J. Mirtazapine and gabapentin for reducing pruritus in cutaneous T-cell lymphoma. J Am Acad Dermatol. 2006; 55:543–544. [PubMed: 16908377]
77. 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. [PubMed: 17058231]
78. Loosemore MP, Bordeaux JS, Bernhard JD. Gabapentin treatment for notalgia paresthetica, a common isolated peripheral sensory neuropathy. J Eur Acad Dermatol Venereol. 2007; 21:1440–1441. [PubMed: 17958872]
79. Sheen MJ, Ho ST, Lee CH, et al. Preoperative gabapentin prevents intrathecal morphine-induced pruritus after orthopedic surgery. Anesth Analg. 2008; 106:1868–1872. [PubMed: 18499625]
80. Goutos I, Clarke M, Upson C, et al. Review of therapeutic agents for burns pruritus and protocols for management in adult and paediatric patients using the GRADE classification. Indian J Plast Surg. 2010; 43:S51–S62. [PubMed: 21321658]
81. Ruiz-Villaverde R, Sanchez-Cano D. Idiopathic senile pruritus: Therapeutic response to gabapentin. Rev Esp Geriatr Gerontol. 2009; 44:355–356. [PubMed: 19720432]
82. Schürmeyer-Horst F, Fischbach R, Nabavi D, et al. Brachioradial pruritus: A rare, localized, neuropathic form of itching [in German]. Hautarzt. 2006; 57:523–527. [PubMed: 15776282]
83. Dereli T, Karaca N, Inanir I, et al. Gabapentin for the treatment of recalcitrant chronic prurigo nodularis. Eur J Dermatol. 2008; 18:85–86. [PubMed: 18086601]
84. Gencoglan G, Inanir I, Gunduz K. Therapeutic hotline: Treatment of prurigo nodularis and lichen simplex chronicus with gabapentin. Dermatol Ther. 2010; 23:194–198. [PubMed: 20415827]
85. Cevikbas F, Seeliger S, Fastrich M, et al. Role of protease-activated receptors in human skin fibrosis and scleroderma. Exp Dermatol. 2011; 20:69–71. [PubMed: 21158940]
86. Karvonen J, Hannuksela M. Long term results of topical trioxsalen PUVA in lichen planus and nodular prurigo. Acta Derm Venereol Suppl [Stockh]. 1985; 120:53–55.
87. Väätäinen N, Hannuksela M, Karvonen J. Local photochemotherapy in nodular prurigo. Acta Derm Venereol. 1979; 59:544–547. [PubMed: 94220]
88. Gambichler T, Hyun J, Sommer A, et al. A randomised controlled trial on photo(chemo)therapy of subacute prurigo. Clin Exp Dermatol. 2006; 31:348–353. [PubMed: 16681573]
89. Hönigsmann H. Mechanisms of phototherapy and photochemotherapy for photodermatoses. Dermatol Ther. 2003; 16:23–27. [PubMed: 12919123]
90. Martínez-Escribano JA, Quecedo E, De la Cuadra J, et al. Treatment of aquagenic urticaria with PUVA and astemizole. J Am Acad Dermatol. 1997; 36:118–119. [PubMed: 8996279]
91. Pothiawala SZ, Baldwin BT, Cherpelis BS, et al. The role of phototherapy in cutaneous T-cell lymphoma. J Drugs Dermatol. 2010; 9:764–772. [PubMed: 20677530]
92. Kaptanoglu AF, Oskay T. Ultraviolet B treatment for pruritus in Hodgkin's lymphoma. J Eur Academy Dermatol Venereol. 2003; 17:489–490.

93. 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. [PubMed: 12410710]
94. Lim HW, Vallurupalli S, Meola T, et al. UVB phototherapy is an effective treatment for pruritus in patients infected with HIV. J Am Acad Dermatol. 1997; 37:414–417. [PubMed: 9308556]
95. Reed J, George S. Pruritic folliculitis of pregnancy treated with narrowband (TL-01) ultraviolet B phototherapy. Br J Dermatol. 1999; 141:177–179. [PubMed: 10417550]
96. Kang MJ, Kim HS, Kim HO, et al. A case of atopic dermatitis-associated lichen amyloidosis successfully treated with oral cyclosporine and narrow band UVB therapy in succession. J Dermatol Treat. 2009; 20:368–370.
97. Oiso N, Yudate T, Kawara S, et al. Successful treatment of lichen amyloidosus associated with atopic dermatitis using a combination of narrowband ultraviolet B phototherapy, topical corticosteroids and an antihistamine. Clin Exp Dermatol. 2009; 34:e833–e836. [PubMed: 20055846]
98. Saltzer EJ, Grove G. Relief from uremic pruritus: A therapeutic approach. Cutis. 1975; 16:298–299.
99. Gilchrest BA, Rowe JW, Brown RS, et al. Relief of uremic pruritus with ultraviolet phototherapy. N Engl J Med. 1977; 297:136–138. [PubMed: 865585]
100. Gilchrest BA, Rowe JW, Brown RS, et al. Ultraviolet phototherapy of uremic pruritus. Long-term results and possible mechanism of action. Ann Intern Med. 1979; 91:17–21. [PubMed: 464448]
101. Lazrak S, Skali H, Benchikhi H, et al. Phototherapy and hemodialysis pruritus [in French]. Nephrologie. 2004; 25:293–295. [PubMed: 15584639]
102. Berne B, Vahlquist A, Fischer T, et al. UV treatment of uraemic pruritus reduces the vitamin A content of the skin. Eur J Clin Invest. 1984; 14:203–206. [PubMed: 6432548]
103. Taylor R, Taylor AE, Diffey BL, et al. A placebo-controlled trial of UV-A phototherapy for the treatment of uraemic pruritus. Nephron. 1983; 33:14–16. [PubMed: 6339963]
104. 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. [PubMed: 14616389]
105. Friedmann PS, Palmer R, Tan E, et al. A double-blind, placebo-controlled trial of montelukast in adult atopic eczema. Clin Exp Allergy. 2007; 37:1536–1540. [PubMed: 17850382]
106. Rahman ML, Choudhury AM, Islam MM. Effectiveness of montelukast in the treatment of atopic dermatitis. Mymensingh Med J. 2006; 15:85–88. [PubMed: 16467770]
107. Mostafa BE, Abdel Hay H, Mohammed HE, et al. Role of leukotriene inhibitors in the postoperative management of nasal polyps. ORL J Otorhinolaryngol Relat Spec. 2005; 67:148–153. [PubMed: 15925911]
108. Di Lorenzo G, Pacor ML, Mansueto P, et al. Randomized placebo-controlled trial comparing desloratadine and montelukast in monotherapy and desloratadine plus montelukast in combined therapy for chronic idiopathic urticaria. J Allergy Clin Immunol. 2004; 114:619–625. [PubMed: 15356567]
109. Woodmansee DP, Simon RA. A pilot study examining the role of zileuton in atopic dermatitis. Ann Allergy Asthma Immunol. 1999; 83:548–552. [PubMed: 10619348]
110. Zabawski EJ Jr, Kahn MA, Gregg LJ. Treatment of atopic dermatitis with zafirlukast. Dermatol Online J. 1999; 5:10. [PubMed: 10673463]
111. Nettis E, Colanardi MC, Soccio AL, et al. Desloratadine in combination with montelukast suppresses the dermographometer challenge test papule, and is effective in the treatment of delayed pressure urticaria: A randomized, double-blind, placebo-controlled study. Br J Dermatol. 2006; 155:1279–1282. [PubMed: 17107402]
112. Nettis E, Colanardi MC, Paradiso MT, et al. Desloratadine in combination with montelukast in the treatment of chronic urticaria: A randomized, double-blind, placebo-controlled study. Clin Exp Allergy. 2004; 34:1401–1407. [PubMed: 15347373]
113. Kesting MR, Thurmüller P, Hölzle F, et al. Electrical ear acupuncture reduces histamine-induced itch (alloknesis). Acta Derm Venereol. 2006; 86:399–403. [PubMed: 16955182]

114. Pfab F, Hammes M, Bäcker M, et al. Preventive effect of acupuncture on histamine-induced itch: A blinded, randomized, placebo-controlled, crossover trial. J Allergy Clin Immunol. 2005; 116:1386–1388. [PubMed: 16337477]

115. Hui KK, Liu J, Marina O, et al. The integrated response of the human cerebro-cerebellar and limbic systems to acupuncture stimulation at ST 36 as evidenced by fMRI. Neuroimage. 2005; 27:479–496. [PubMed: 16046146]

116. Gupta MA, Gupta AK. Stressful major life events are associated with a higher frequency of cutaneous sensory symptoms: An empirical study of non-clinical subjects. J Eur Acad Dermatol Venereol. 2004; 18:560–565. [PubMed: 15324393]

117. Stangier U, Ehlers A, Gieler U. Predicting long-term outcome in group treatment of atopic dermatitis. Psychother Psychosom. 2004; 73:293–301. [PubMed: 15292627]

118. Staab D, Diepgen TL, Fartasch M, et al. Age related, structured educational programmes for the management of atopic dermatitis in children and adolescents: Multicentre, randomised controlled trial. BMJ. 2006; 332:933–938. [PubMed: 16627509]

119. Weisshaar E, Diepgen TL, Bruckner T, et al. Itch intensity evaluated in the German Atopic Dermatitis Intervention Study (GADIS): Correlations with quality of life, coping behaviour and SCORAD severity in 823 children. Acta Derm Venereol. 2008; 88:234–239. [PubMed: 18480921]

Table 1

Considerations from the Patient's History That Can Help Explore the Underlying Cause of Itch

Itch With or Without Skin Lesions?
Primary or secondary itch lesion? Distribution? Morphology?
Alloknesis?
Dermographism: White? Red? Urticarial?
Quality and quantity (on a scale from 0 to 10) of the itch?
Impact on the quality of life?
Allergies (subtype?)
Medications?
Age (Xerosis? Morbus Grover, Neuropathy? Neurodegeneration? Metabolic? Diabetes? Cancer? Infection? Immunosuppression?)
Trigger factors: Temperature changes? Water? Chemicals? Haptens? Medication?
Signs for systemic cause? (e. g. cholestasis, jaundice, weight loss, other signs for neoplasia or paraneoplastic syndrome, compression of nerves or other neurological symptoms, signs for a psychiatric disease; anemia?)
One or more causes likely? (e. g. atopic dermatitis and xerosis, psoriasis and medication etc.).

Table 2

Potential Topical Strategies Targeting Different Pathophysiology of Itch

Vehicle (biophysical and chemical resaturation of the skin): acute: lotion, foam, cream; chronic: ointment, modern creams based on nanotechnological improvements, foam (scalp)
Anti-Inflammatory: topical glucocorticosteroids, topical calcineurin inhibitors
Cooling agents, neural modulation: menthol, camphor, ice, topical anesthetics
Non-inflammatory, neuro-modulating (ion channels): capsaicin, ketamine
Predominantly nerve modulation (neurotransmitters): doxepin, topical amitriptyline

Table 3

Early-Phase Treatment of Potentially Histamine-Mediated Chronic Itch*

Itch at daytime: start with low-dose antihistamine, followed by high-dose antihistamine, prefer nonsedative AH.
Itch at nighttime: start with sedative antihistamine (consider side effects: antimuscarinergic, prostate enlargement; interaction with TCA or TTCA; potentiates anti-muscarinergic effects).
Itch at daytime and nighttime: start with high-dose nonsedative antihistamine at daytime, sedative antihistamine at night time.
Atopic dermatitis: start with high-dose nonsedative antihistamine at daytime, sedative antihistamine at night (eg, fexofenadine 180 mg morning, cetirizine 10 mg noon and evening, sedative antihistamine at night). Consider contraindications and side-effect profile. Do not use without antiinflammatory topical and anti-xerotic therapy.

* This algorithm is based on current literature about effectiveness in clinical trials, reports, and consideration of pharmacological aspects and side effect profiles.

Table 4

Possible Therapeutic Ladder from Single to Combination Therapy in Patients with Chronic Pruritus Responding to Anti-Histamines at Various Doses or Combinations

Level I: Histamine-Mediated Chronic Pruritus				
Low Dose	→	**High-Dose**	→	**Combination (anti-histamine with other systemics)**[†]
Non-sedative AH, daily (usually single agent)[*]		AH, bid-qid (usually combination of different AH)[*]		Combination of different AH, bid-qid, plus: CU: Dapson (50–150 mg/d) or LRA (e.g. monteleukast, daily) AD: systemic antiinflammatory and/or anti-pruritic therapies[‡] Neuropathic: Gabapentin (900–3600 mg/d) or SSRI or TCI or TTCI
CU		CU		CU
		AD		AD
		Idiopathic		Idiopathic Refractory itch

Examples: start with low dose in chronic urticaria, start with high dose in AD, idiopathic itch; start with combination therapy in refractable itch. In certain diseases, see Table 2; it does not make sense to start with antihistamines or combinations at all.

Level 1 indicates histamine-mediated diseases.

AD, atopic dermatitis; AH, anti-histamine; CU, chronic urticaria; LRA, leukotriene receptor antagonist; SSRI, selective serotonin reuptake inhibitor; TCI, Tricyclic antidepressant; TTCI, tetracyclic antidepressant.

[*] See text for details on the use of single-dose vs. high-dose therapy.

[†] Consider: age, renal function, arrythmia risk, sedation, drug interactions.

[‡] See text for details.

Table 5

Inflammatory, Immune-Mediated Pruritic Diseases, Where SGC May Be First-Line Therapy (Examples)

Level II: Non-Histamine-Mediated Chronic Pruritus
Systemic glucocorticosteroids* (start with 0.5 – 1 mg/kg b.w., taper down dependent on clinical appearance)
Indications:
Bullous pemphigoid (start with class I topical steroid)
Drug-induced hypersensitivity syndrome (attempt to taper down quickly, but longer therapy may be required)
Lupus erythematosus-associated itch/burning
Severe sunburn

Note that AD is not included, and that in many diseases SGC are even not second- or third-line therapy. In many instances of mentioned first-line indications, class 1 topical GCs have been demonstrated same efficacy with less side effects. When compliance is given, TGCs are preferred because of a weaker side effect profile.

AD, atopic dermatitis; CU, chronic urticaria; HES, hydroxy-ethyl starch; SGC, systemic glucocorticosteroids; TCI, tricyclic anti-depressant; TTCI, tetracyclic antidepressant.

*Addition of GC-sparing agent should be considered if duration of SGC treatment exceeds four to six weeks.

Table 6

Possible Therapeutic Ladder for Refractory Chronic Pruritus, Pruritus of Unknown Origin or When Diagnostics Not Conclusive

Level III. Refractory chronic pruritus, itch of special types, pruritus of unknown origin or when diagnostics not conclusive:			
1st	**2nd***	**3rd***	**4th**
Gabapentin and pregabalin	SSRI†	Naltrexone	IVIG
(*Other 1st line indications*):	TCI	(1st line when: - HES-induced itch)	EP
Neuropathic: e.g. post-herpetic	TTCI	Lidocaine 5% patch	
Small fiber neuropathy	Phototherapy		
Notalgia paraesthetica			
Brachioradial pruritus			
Prurigo			
Scalp Itch			
Genital itch			
Post-burn itch			
SSRI (before gabapentin, when):			
Paraneoplastic			
Polycythemia vera			
plus Depression			
Naltrexone (before gabapentin or pregabalin, when):			
Renal dysfunction-related itch			
Liver dysfunction-related itch			

1st, first-line, 2nd, second-line, 3rd, third-line therapy; AD, atopic dermatitis; CU, chronic urticaria; HES, hydroxy-ethyl starch; IVIg, intravenous immunoglobulins; ectracorporal photopheresis. TCI, tricyclic antidepressant; TTCI, tetracyclic antidepressant.

*We prefer combination of first- and second-line therapy ("add-on") rather than replacement. Treatment modality for gabapentin is primarily neuropathis, but - as seen from the table - is not limited to neuropathic diseases.

†For differences between SSRi, TCI, and TTCI, see text.

Table 7

Examples of Used Antipruritic Antidepressants (APAD) in Itch Therapy

	SSRI	SNRI	TCA	TTCA
Example	Fluoxetine	Venlaxafine	Amitriptyline	Mirtazepine
	Paroxetine	Duloxetine	Imiprmaine	
	Sertraline		Clomiprmaine	
	Venlaxafine		Doxepin	
SE	Anxiety	Anxiety	Anti-muscarinic	Weight gain
	Agitation	Agitation	α-adr blockage (coma) (seizures)	
	Sexual dysfunction	Increased/decresed libido	Arrythmia risk	
	Weight-loss	Weight-loss	Sexual dysfunction	
	Insomnia	Insomnia	Hypotension	
Do not Combine With	MAO-inhibitor	SSRI	SSRI, SNRI	
	TCA meperidine		MAO-Inhibitor a2-adrenergics	

Side effect (SE) profiles and unsafe combinations have to be considered, especially in older patients.

For abbreviations, see Table 6

Table 8

Medical Conditions in Which Thalidomide Could Be Considered as a First- or Second-Line Therapy

Reported as effective, when other therapeutic regimens fail:
Prurigo nodularis (when refractory)
Actinic prurigo
CDLE
Cancer-associated itch

CDLE, chronic discoid lupus erythematodes.