

Reviews

Itch – an update

Gil Yosipovitch¹

Sri Lanka Journal of Dermatology, 2003, 7, 3-12

Abstract

Itch is the most common symptom in dermatology and has a significant impact on the quality of life of our patients. Significant progress has been achieved in understanding the pathophysiology of itch in the last 7 years. The purpose of this review is to bring the reader up to date on recent advances in pathophysiology, diagnosis, and management of itch. It describes a clinical classification of itch, based upon improved understanding of the neurophysiology of itch. The review also seeks to point up rational approaches to treatment in the light of these developments. It also describes itch characteristics in Asian populations which are not well addressed in the literature as well as unique types of itch such as neuropathic itch.

Itch was defined more than 340 years ago by Samuel Haffnerfer as an "unpleasant sensation provoking the desire to scratch". This definition does not cover all the aspects of this subjective symptom but provides a simple and accurate description of itch.

Pathophysiology of pruritus

Itch has declared its independence from pain in a pivotal study by Schmelz et al. in 1997¹ who used direct nerve recordings in awake humans and demonstrated that itch is transmitted by dedicated C neurons distinct from the classical "polymodal nociceptors" which are involved in pain processing. These "itch" neurons can be identified by their lasting response to histamine application and are characterized by their slow conduction velocities and extensive terminal branching². In a recent study the same C fibers have shown spontaneous activity in a patient suffering from chronic itch³. The concept of dedicated itch neurons has now been complemented and extended by studies of recordings from the cat spinal cord. A specific class of dorsal horn neurons projecting to the thalamus has been demonstrated which responds selectively to histamine iontophoretically administered to skin⁴. The time course of these responses was similar to that of itch sensation in humans and matched the responses of the distinct peripheral C fibres which transmit itch. However, it should be made clear that there is no single specialized itch receptor

on peripheral nerve endings. The specificity of itch neurons is therefore based on their spinal connections to the itch pathway, rather than on unique peripheral receptors.

The supraspinal processing of itch and its corresponding scratch response have recently been investigated in man by functional positron emission tomography (PET) as well as functional MRI^{5,8}. Induction of itch by intradermal histamine injections and histamine skin prick elicits co-activation of sensory as well as motor areas in the brain. The significant co-activation of the motor area supports the clinical observation that itch is inherently linked to a desire to scratch.

Mediators for itch other than histamine: tryptase, neuropeptides, opioid peptides, serotonin, cytokines and prostaglandins in pathophysiology of itch

Histamine is the most known mediator of itch. It clearly is an important mediator of itch in urticaria however in itch related to chronic pruritus associated with other skin inflammatory diseases such as atopic eczema and in systemic diseases its role is very limited. This explains the weak therapeutic efficacy of antihistamines as anti pruritics.

Proteinases such as trypsin, chymotrypsin and papain have been for decades suggested as mediators of itch⁹. Recent studies have shown that activation of the mast cell releases a proteinase named tryptase, which in turn activates a proteinase activated receptor - 2 (PAR-2) localised on C fibre nerve terminals as well as keratinocytes¹⁰. The activated C fibers will transmit this information to the central nervous system, inducing the sensation of itch. Several studies suggested a role of tryptase in itch in atopic dermatitis¹¹⁻¹². Steinhoff et al.¹³ demonstrated enhanced tryptase immunoreactivity in lesions of atopic dermatitis patients in comparison to healthy controls. Accordingly the PAR-2 receptor for tryptase was markedly enhanced. No differences in histamine concentration was noted between the 2 groups. Thus tryptase and its receptor PAR-2 may be involved in

¹ Associate Professor of Dermatology, Department of Dermatology and Neuroscience Center, Wake Forest University Medical Center, Winston Salem NC 27157, U.S.A.

itch responses in atopic dermatitis and other inflammatory skin diseases.

It is well known that neuropeptides such as substance P (SP), provoke itch associated with erythema, wheal and flare, i.e. neurogenic inflammation¹⁴. Direct communication between nerve fibers and mast cells via SP has been verified¹⁵. The proximity of dermal mast cells to afferent C neuron terminals in skin suggests a functional relationship between these two cells.

Opiates and itch: Opiates have a direct central and peripheral itch producing activity. Low doses of intradermal morphine produce itch, and the effect is independent of mast cell degranulation. This effect is probably caused by μ -opiate receptors, as it has been reported that the μ -opiate receptor antagonist naltrexone suppresses these itch sensations. In addition, it was recently reported that the activation of κ -opiate receptor antagonizes various μ -opiate receptor mediated actions. Togashi et al.¹⁶ reported that a novel κ -receptor agonist (TRK-820) when administered subcutaneously or orally, reduces scratching in a mouse model for pruritus.

Serotonin: When serotonin is injected intradermally or induced by iontophoresis, it induces itch, but is less potent than histamine⁹. It also may have a role in opioid central itch, since greater central opioid tone can cause increased serotonergic tone. Recently controlled trials using Serotonin 3 receptor antagonists have shown no significant effects in renal itch¹⁷.

Cytokines and pruritus: Cytokines have been proposed as mediators of non-histamine induced itch. Only IL-2 shows a direct pruritogenic effect when it is injected intradermally¹⁸. Although TNF alpha does not have any direct pruritogenic effect, it is elevated in many pruritic dermatoses and antipruritic medications such as thalidomide may exert their anti pruritic effect by lowering TNF alpha levels. Recent studies have shown a role of IL-6 and IL-4 in the elicitation of itch²¹⁹.

Prostaglandins and leukotrienes: Prostaglandins do not have a direct pruritogenic effect on itch, but are known to lower the skin threshold for itch induced by histamine and most probably other mediators²⁰. Recent studies have shown that leukotriene B₄ may elicit itching and scratching through the activation of LTB₄ receptors²¹.

Different types of itch

Recently a definition of different types of itch was described²²⁻²³. This may help us to evaluate and treat

pruritus in a more meaningful way both for the individual patient and also for the comparison of potential therapies in studies.

Pruritoceptive: Pruritus originating in the skin due to inflammation, dryness or other skin damage. Examples include itch due to xerosis, eczema, urticaria, insect bite reactions and scabies.

Neuropathic pruritus: Pruritus which is due to pathology located at any point along the afferent pathway. Examples include post-herpetic neuralgic itch, brachioradial pruritus, pruritus due to hydroxyethyl infusion, itch associated with multiple sclerosis and cerebral vascular events.

Neurogenic pruritus: Pruritus that originates centrally but without evidence of neural pathology, exemplified by itch of cholestasis due to the action of opioid neuropeptides on opioid receptors.

Psychogenic pruritus²⁴: Pruritus associated with psychologic abnormalities, for example in a delusional state of parasitophobia, or itch in a compulsive disorder.

However, there is no reason why one type of pruritus may not coexist concurrently with another in a given patient. For example, in a patient with prurigo nodularis there could be both pruritoceptive itch and neuropathic itch.

There are several other definitions which are important when discussing itch²⁵. **Chronic pruritus:** Chronic itch is a prolonged itch which lasts weeks, months or years. Chronic itch will continue when treatment stops. It has a significant impact on quality of life. It sometimes may totally destroy a patient's social life and lead to suicide as with patients who have chronic pain. Because chronic pruritus is unrelenting, it is likely that stress, affective factors and environmental factors such as heat and dryness may be superimposed on the original damaged tissue and contribute to the intensity and persistence of pruritus. Medical treatment can be helpful to prevent or reduce the itch and to shorten the duration of inflammation.

Another form of itch in chronic sufferers is **intractable pruritus**, which is an itch that cannot be treated in the generally accepted course of medical practice. It is important to acknowledge that such patients are encountered weekly in dermatology clinics and they do suffer. In these cases a more holistic approach is required by an interdisciplinary team, with involvement of both patients and their families. It integrates pharmacologic and non-pharmacologic treatment with needed psychotherapy, and rehabilitation.

Pruritus in skin disease could be also divided into two subcategories: **localized** such as in contact

dermatitis and lichen simplex chronicus, and generalized such as erythroderma, atopic eczema, and senile xerosis.

Chronic itch and quality of life: Chronic itch has a significant toll on the quality of life of patients. It causes depression and low self esteem and effects the patients daily life. In atopic dermatitis, psoriasis and chronic urticaria the patients reported significant impact of itch on their daily life²⁶⁻²⁸. In most inflammatory skin diseases and systemic diseases pruritus is exacerbated at night and impairs sleep²⁹, possibly due to circadian rhythms of secretion of mediators involved in itch.

Specific entities which are more common in Asians where itch is a major symptom: Hypertrophic scars and keloids: Keloids and scars can cause itch, especially in those which are growing³⁰. In a recent survey of 60 Asians who suffered from keloids of 2 cm and above, 90% of the patients complained of pruritus, especially at the borders of the keloid. (Yosipovitch, unpublished results). Interestingly, the patients occasionally suffer simultaneously from pain, usually in the center of the keloid, and pruritus in the borders (Lee, Yosipovitch unpublished data).

Lichen amyloidosis (LA): This is a form of primary localized cutaneous amyloidosis, characterized by the clinical appearance of brownish lichen if red papules. This condition is associated frequently with severe localized pruritus³¹. LA usually presents as an idiopathic hyperpigmented papular eruption which occurs symmetrically predominantly on the extensor surfaces of the extremities and back. There are reports of LA appearing at the nipples and vulva and a generalized form has also been recognized³²⁻³³. Pruritus may be a presenting symptom. There had been some suggestion that itch induces the clinical lesions and some clinicians consider LA to be a variant of lichen simplex chronicus³⁴. The disorder is seen in all racial groups but seems more common in Hispanics and Asians³¹.

Clinical features and epidemiology of neuropathic pruritus:

Post herpetic pruritus (PHI)

Post herpetic pruritus can be part of post herpetic neuralgia³⁵⁻³⁶. A recent study reported that among 153 patients with prior shingles, 48% reported itching on the McGill pain questionnaire³⁷. PHI could occur in the same location and time as PHN³⁸. Interestingly, most cases of PHI were on the face³⁹. In these patients

itch can coincide with pain in the same site this phenomenon is not observed in itch related to inflammatory skin diseases or in neurogenic itch related to uremia, or cholestasis.

Notalgia paresthetica: Notalgia paresthetica (NP) is a syndrome of localized pruritus in which patients present with itching of the back in the distribution of T2-T6 dermatomes⁴⁰. It is usually unilateral. Other sensory symptoms, such as numbness, tingling may be present as well. Usually there is no visible abnormality of the skin, but in chronic cases secondary changes caused by rubbing and scratching may occur. Some cases of macular amyloidosis of the upper back are related to underlying NP⁴¹.

Compression of posterior rami of spinal nerve roots T2-T6 is thought to be involved in NP⁴². Many cases of NP are associated with radiographic abnormalities of the spine, which in turn may be related to nerve compression⁴²⁻⁴³. These abnormalities correlated precisely with the dermatomal localization of pruritus⁴⁴.

Brachioradial pruritus: Brachioradial pruritus (BRP) is a syndrome of localized pruritus in which patients present with itching localized to the brachioradial area of the arm and often seek the advice of a dermatologist. Pruritus sometimes extends across the back and occasionally the chest⁴⁵. BRP has been related to cervical root compression including a spinal cord tumor, involving one or all of C5-C8 cervical nerve root segments⁴⁶. Patients suffered from altered sensation in the same dermatome where pruritus was present^{47,48}. In a recent study of 22 patients with BRP 11 patients underwent radiographs of the cervical spine⁴⁹. Each of these eleven patients had cervical spine disease that could be correlated with the location of their symptoms. Heyl⁵⁰ suggested that cervical spine X-rays should be obtained in any patient who complains of BRP. A recent study demonstrated abnormal electrophysiologic studies of the median, ulnar, and radial nerves in patients with BRP⁵¹.

Some investigators believe that BRP is a result of solar exposure and have called BRP "solar pruritus"⁶⁰. Bernhard suggested that both cervical spine disease and sun-induced cutaneous nerve injury are important contributors acting to variable degrees in individual patients⁴¹.

Pruritus due to pathology in the Brain: Pruritus has been reported as a manifestation of brain pathology. The list of underlying pathologies includes strokes⁵²⁻⁵⁴, tumors⁵⁵ abscesses⁵⁶ and Creutzfeldt-Jakob disease⁵⁷. In fact, pruritus can present as the first and only symp-

tom of a brain tumor⁵⁵. It can also be the first symptom of Creutzfeldt-Jakob disease⁵⁷.

Facial and/or nasal pruritus is a particularly interesting manifestation of brain tumors⁵⁸. Complete resolution of pruritus was observed in some cases once the tumors were treated. Paroxysmal itching has been described in patients with multiple sclerosis⁵⁹. The itching may be in any part of the body and can be very intense. The attacks can last from several seconds to a few minutes and may occur several times a day. Attacks often awaken the patient from sleep⁶⁰. Episodes may be spontaneous or triggered by a bath or sudden movement.

Methods to evaluate itch

The multidimensional nature of itch, including its complex qualitative temporal and spatial components, provides a more in depth understanding of the troublesome symptom. Recently two itch questionnaires were published which help assess these components. Both are based upon the well-recognised McGill pain questionnaire and both have been validated⁶¹⁻⁶². Information from a well constructed questionnaire is valuable in diagnosis and in optimizing treatment⁶³.

In a research setting, indirect objective correlates are often used, based upon the assumption that scratch = itch. Methods include an infrared camera to take time-lapse exposures of nocturnal itching⁶⁴, piezoelectric transducer devices attached to finger nails and limb movement meters⁶⁵⁻⁶⁷. These are not necessarily more valuable than the traditional visual analogue scale which allows the subject to quantify itch subjectively and quite accurately⁶⁸.

Management

Better understanding of the pathophysiology of itch and the different types of itch has led to modest advances in treatment of itch summarized below. In time this progress will perhaps to long-awaited selective topical and systemic antipruritics.

Antipruritic strategies could be assigned according to the proposed classification of itch.

Treatment of pruritoceptive itch

Therapeutics mainly targeting pruritoceptive itch consist of topical modalities like emollients, counter irritants, topical anesthetics, topical corticosteroids, capsaicin, topical antihistamines, topical immunomodulators, topical non steroidal anti-inflammatories, herbal remedies⁶⁹.

Emollients: Although emollients are not anti-pruritic per se, they have been commonly used for decades. In addition, they can help restore the barrier function, especially in patients where itch is related to skin xerosis and pruritoceptive itch, and where the barrier function is damaged. In Europe there are several compounds used which contain polidocanol which has local anesthetic properties and a moisturizing effect. It is frequently used in children and has also been reported to relieve uremic itch⁷⁰. In the US new formulations containing Dominant ceramides which replenish the stratum corneum natural moisturizing factor may have anti-pruritic effect⁷¹.

Coolants and counter irritants as anti pruritics: These over-the-counter agents are time-honoured antipruritics. They are commonly used all over the world and especially in Asia and in different preparations and concentrations. Most of these products contain menthol, camphor and phenol. Their antipruritic effect is exerted by inducing a counter-irritation to cool the skin and by a direct effect on delta-A fibers that transmit the sensation of cold and mask the sensation of itch transferred by C nerve fibers. There are few scientific studies that examined their effect on itch. In a single-blind study 10% menthol had no antipruritic effect⁷². However, Bromm et al. found an antipruritic effect with lower concentrations⁷³.

Topical anesthetics: Topical pramoxine, which has local anesthetic properties, has been widely used as an antipruritic for decades. We have previously shown that topical application of pramoxine can significantly benefit histamine-induced pruritus⁷⁴. EMLA cream has been shown to reduce histamine induced itch⁷⁵.

Topical corticosteroids provide symptomatic relief of pruritus related to inflammatory skin diseases, however they are not direct antipruritics and should not be used as such.

Topical antihistamines: Several topical H1 antihistamines are available.

Because of its exceptionally high potency as an antihistamine, the tricyclic compound doxepin has been formulated as a topical medication. It has been proven as an antipruritic in a vehicle-controlled double blind trial⁷⁶. However, its value is limited by sedation due to percutaneous absorption and high incidence of allergic contact dermatitis⁷⁷.

Capsaicin: This is the active ingredient of chili and owes its antipruritic properties to desensitization of nociceptive nerve endings. It is especially useful in

concentrations of 0.025-0.075% in localized intractable pruritus⁷⁸. It is also effective in pruritus of atopic eczema, but its value is limited by production of irritation at the site of application. Although this diminishes after repeated use, it reduces patient compliance. This unwanted side effect can be reduced by using the topical local anaesthetic EMLA (eutectic mixture of local anaesthetics)⁷⁹.

Topical immunomodulators: Immunomodulators such as tacrolimus and pimecrolimus which inhibit T cell activation have demonstrated indirect antipruritic activity by decreasing the signs and symptoms of atopic dermatitis⁸⁰⁻⁸¹. It seems that tacrolimus is a more potent drug than pimecrolimus in inhibiting itch in atopic dermatitis patients. Recent studies have demonstrated that topical tacrolimus clearly reduced itch severity in atopic dermatitis⁸².

Aspirin: Prostaglandins are known to contribute to histamine induced pruritus by lowering the skin threshold for itch⁸³. Although oral administration of aspirin seems to have little or no effect on clinical itch⁸⁴, topical aspirin has been found to have an anti pruritic effect in experimentally induced itch⁸⁵. Recently a vehicle controlled double blind crossover trial confirmed its effect in patients with severe lichen simplex chronicus, a form of localized itch⁸⁶.

Herbal remedies with anti inflammatory and anti itch properties

A new topically active antipruritic derived from the Amazonian medicinal *sangre de grado* has been recently described⁸⁷. The reported antipruritic effect on itch induced by insect bites was convincing. But further clinical studies are needed to evaluate its role in patients with chronic itch.

Strontium nitrate: Topical 10-20% strontium salts, which are naturally present in green leaves suppress histamine induced itch and are used for treatment of post peeling itch⁸⁸.

Phototherapy

Phototherapy with PUVA, narrow band UV-B and UV-B has been shown to be effective in itch associated with atopic eczema, uremic itch and HIV disease⁸⁹. Patients can be treated from 3 times per week with PUVA and narrow band UV-B, to up to 5 times per week with UV-B. It should be noted that one of the side effects in patients treated with these methods, and especially those treated with UV-B, is itch. Although not subjected to any controlled trial, it seems

that treatment with narrow band UV-B has similar efficacy to PUVA and causes less itch than UV-B therapy.

Systemic treatment for pruritoceptive itch

Antihistamines: Oral antihistamines have been used for decades to treat itch and are still the most commonly prescribed treatment for itch. However their efficacy, except in cases of urticarial itch, is limited. The traditional H1 antihistamines are the most effective, especially hydroxyzine, due to their side effect of sedation. This seems to play a significant role in alleviating nocturnal itch. The second generation oral antihistamines such as loratadine and terfenadine do not seem to have any effect on itch except in histamine induced itch such as urticaria and insect bite reactions⁹⁰. Third generation antihistamines such as desloratadine have comparable efficacy for itch related to chronic urticaria to first generation H1 antihistamines but less adverse effects⁹¹.

Thalidomide: Thalidomide has shown antipruritic efficacy in treating inflammatory skin diseases such as prurigo nodularis, actinic prurigo, eczema, and senile pruritus⁹²⁻⁹³. The antipruritic activity could be related to several mechanisms. An antipruritoceptive effect is one possibility, since it inhibits TNF alpha synthesis. Another mechanism is due to its direct effect on peripheral nerves and a central nerve depressant⁹².

Treatment of neuropathic itch

Therapeutic options for *neuropathic* itch are sparse. Drugs proven to be effective in neuropathic pain, such as lidocaine and the anticonvulsant gabapentin have been claimed to be effective. The dose of gabapentin can be as high 2400mg/day. Treatments for Brachioradial pruritus include physiotherapy, neck traction and cervical spine manipulation⁵⁰, topical capsaicin⁹⁴⁻⁹⁵, gabapentin⁹⁶, anti-inflammatory drugs⁵⁰, and surgical resection of a cervical rib⁹⁷.

Reported treatments for *notalgia parasthetica* (NP) include physiotherapy⁴², paravertebral local anesthetic blocks⁹⁸, cervical epidural steroid injection⁴⁴, EMLA cream⁹⁹, and Capsaicin¹⁰⁰. Most of the above treatments exert their effect through actions on the nervous system. This supports the hypothesis that pruritus in NP is of neurologic origin. Recently a 5% lidocaine patch was reported to alleviate an intractable central neuropathic itch related to a tumor in the spinal cord¹⁰¹.

Treatment of neurogenic pruritus: Therapeutic options for neurogenic itch are mainly based on the antagonistic interaction between itch and pain on a spinal level. The inhibition of itch by pain has been successfully used to suppress experimental itch. Several studies demonstrated that different opioid receptor antagonists may significantly diminish pruritus¹⁰². Naltrexone and nalmefene are two oral opiate antagonists which can be used as effective antipruritics, especially in cholestatic pruritus¹⁰³.

Naltrexone is an orally active, long acting, competitive antagonist at μ -opioid receptors.

Nalmefene, a chemical analogue of naltrexone and is a potent, orally active opioid antagonist at μ -receptor. Nalmefene has several pharmacological advantages over naltrexone e.g. prolonged duration of action and increased potency at the opioid receptor level.

Naltrexone and nalmefene are contraindicated in patients with liver disease. In liver cirrhosis, metabolism of naltrexone into 6 β -naltrexol is disturbed, leading to minor effective circulating concentrations. Furthermore, naloxone, naltrexone and nalmefene must not be used in drug addicts and in patients receiving opioid analgesics and opioid containing medicines such as cough, and anti-diarrheal preparations.

The main side-effects are nausea, vomiting, fatigue, dizziness and less frequently chills, loss of appetite, heart-burn, diarrhoea, myalgia, arthralgia, fever, or headache¹⁰².

Naltrexone 50 mg daily was given in an open label clinical trial to 50 patients with pruritus of various etiologies including internal disease and different inflammatory skin diseases such as prurigo nodularis. A significant therapeutic response was achieved in 35 of the 50 patients in 1 week¹⁰³. Nalmefene, in doses ranging between 40-240 mg, has been shown to reduce scratching activity significantly in patients with cholestasis and pruritus.

Opioid antagonists in the treatment of uremic pruritus: Although naltrexone has been reportedly effective in decreasing pruritus in a short term study (1 week)¹⁰⁴, no effect was noted in a larger randomized placebo-controlled crossover study for 4 weeks¹⁰⁵.

Promising results have been recently presented with a new oral drug TRK 820 which is a κ -opioid agonist¹⁰⁶ that had an antipruritic effect in uremic pruritus patients¹⁰⁷.

Empiric therapeutic approaches for uremic and hepatic pruritus

Several therapeutic interventions, other than opiate antagonists, have been used empirically in the treatment of pruritus complicating liver disease and chronic uremia. These approaches lack a clear scientifically sound rationale and the efficacy of none of them has been established in well-designed clinical trials nor confirmed in subsequent trials. **Bile acid resins:** Cholestyramine and colestipol are anion exchange resins that bind anions (including bile acids) in the intestine, and decrease their enterohepatic circulation. Pruritus in some patients with liver disease appears to respond to treatment with one of these resins¹⁰⁸⁻¹⁰⁹. An improvement, if it occurs, tends to be transient. **Rifampicin:** At doses of 300-450 mg/day, appeared to be associated with an improvement of the pruritus of cholestasis¹¹⁰⁻¹¹¹. **5-HT₃ receptor antagonists:** Several reports demonstrated benefit from the use of 5-HT₃ receptor antagonists in cholestatic as well as uremic types of pruritus and opioid induced pruritus. The dosages were 8 mg intravenous or orally. However in controlled studies odansterone did not demonstrate any antipruritic effect¹⁷.

Miscellaneous techniques targeting nerve fibers transmission of itch

Cutaneous nerve stimulation: This technique electrically stimulates the afferent nerve fibers to inhibit histamine-induced itch in healthy volunteers¹¹². This study led to an open label study in 19 patients suffering from severe localized itch, the results showed significant reduction in severity of itch¹¹³. It is suggested that these type of procedures act through endogenous central inhibitory mechanisms that are normally activated by scratching the skin.

Treatment of psychogenic itch

Anti-depressive drugs such as serotonin reuptake inhibitors (SSRI) and tricyclic compounds such as Doxepin have antipruritic effects and have a beneficial effect on psychogenic itch¹¹⁴. From our clinical experience, patients who had persistent itch related to obsessive compulsive disorders and depression significantly improved with SSRI; especially the new medications such as sertraline. The new SSRI mirtazapine exerts dual antidepressant action on both noradrenergic and serotonergic neurotransmitter systems. It has a lower incidence of the side effects typically associated with SSRIs, such as sleeping disorders and sexual dysfunction, which makes it a favorable drug. Several patients with psychogenic itch who did not report any benefit from oral Doxepin, and SSRIs such as sertraline and paroxetine re-

sponded extremely well to 15 mg mirtazapine once daily. We have recently used this drug also for several patients with severe nocturnal pruritus associated with atopic eczema and prurigo nodularis. Our results demonstrated significant reduction of itch in those patients. Currently there are no controlled studies examining the effect of any of these drugs on itch.

Antipsychotic medications are useful for the treatment of delusions of parasitosis. The current drug of choice is Pimozide¹¹⁵. Effective doses usually range from 1-10 mg/day. The most common adverse effects are extrapyramidal reactions such as stiffness, akathisia and tardive dyskinesia, which is irreversible. Diphenhydramine, 25 mg 3 times daily, could be added to prevent the extrapyramidal signs. Dermatologists treating their patients with this drug should use the lowest effective dosage for the shortest possible duration to minimize the risk of tardive dyskinesia. New antipsychotics such as risperidone, which have a much safer adverse effect profile, may prove to be effective for this psychotic syndrome.

Complementary management

Patients with chronic pruritus due to psychogenic itch, as well as skin diseases such as atopic dermatitis and psoriasis often respond to stressful events with increased pruritus. Psychological counseling and management of emotional or psychological problems contributing to their symptoms may be of great help.

In conclusion, the increase in our knowledge of the pathophysiology of itch as well as understanding the clinical types of itch will eventually lead to development of new therapeutic strategies for the benefit of our patients. Combining treatments in patients with chronic itch, which inhibit itch transmission in the central nervous system with topical or oral treatments inhibiting inflammatory mediators seem to be effective in reducing the intensity of this bothersome symptom.

References

- Schmelz M, Schmidt R, Bickel A et al. Specific C receptors for itch in human skin. *J. Neurosci* 1997; **17**: 8003-8008.
- Stander S, Steinhoff M, Schmelz M et al. Neurophysiology of pruritus. Cutaneous elicitation of itch. *Arch Dermatol* 139; 1463-1470.
- Schmelz M, Hilliges M, Schmidt R et al. Active "itch fibers" in chronic pruritus. *Neurology* 2003; **61**: 564-566.
- Andrew D, Craig AD. Spinothalamic lamina I neurons selectively sensitive to histamine: a central neural pathway for itch. *Nat Neurosci* 2001; **4**: 72-77.
- Hsieh JC, Hagermark O, Stahle-Backdahl M, et al. Urge to Scratch represented in the human cerebral cortex. *J Neurophysiol* 1994; **72**: 3004-3008.
- Darsow U, Drzezga A, Frisch M et al. Processing of histamine-induced itch in the human cerebral cortex: a correlation analysis with dermal reactions. *J Invest Dermatol* 2000; **115**: 1029-1033.
- Drzezga A, Darsow U, Treede RD et al. Central activation by histamine-induced itch: analogies to pain processing: a correlational analysis of O-15 H₂O positron emission tomography studies. *Pain* 2001; **92**: 295-305.
- McGlone F, Rukwied R, Hitchcock D et al., Histamine induced discriminative and affective responses revealed by functional MRI. in: *Itch Basic Mechanisms and Therapy* Yosipovitch G, Greaves MW, Fleischer AB, McGlone F, Eds. Merckel Dekker 2004 pp51-61.
- Hagermark O. Itch mediators. *Semin Dermatol* 1995; **14**: 271-6.
- Steinhoff M, Vergnolle N, Young SH et al. Agonists of proteinase-activated receptor 2 induce inflammation by a neurogenic mechanism. *Nat. Med* 2000; **6**: 151-158.
- Steinhoff M, Corvera CU, Thoma MS et al. Proteinase-activated receptor-2 in human skin: tissue distribution and activation of keratinocytes by mast cell tryptase. *Exp Dermatol* 1999; **8**: 282-294.
- Jarvikallio A, Naukkarinen A, Harvima IT et al. Quantitative analysis of tryptase- and chymase-containing mast cells in atopic dermatitis and nummular eczema. *Br J Dermatol* 1997; **136**: 871-877.
- 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.
- Hägermark, Ö., Hökfelt, T. and Pernow, B.: Flare and itch induced by substance P in human skin. *J Invest Dermatol* **71**: 233-5, 1978.
- Suzuki R, Furuno T, McKay DM, et al. Direct neurite-mast cell communication in vitro occurs via the neuropeptide substance P. *J. Immunol* 1999; **163**: 2410-2415.
- Togashi Y, Umeuchi H, Okano K, et al. Antipruritic activity of the kappa-opioid receptor agonist, TRK-820. *Eur J Pharmacol* 2002; **435** (2-3): 259-64.
- Weisshaar E. 5HT₃ receptor antagonists as antipruritics. in: *Itch Basic Mechanisms and Therapy* Yosipovitch G, Greaves MW, Fleischer AB, McGlone F, Eds. Merckel Dekker 2004 pp 325-334.
- Wahlgren CF, Tengvall Linder M, et al. Itch and inflammation induced by intradermally injected interleukin-2 in atopic dermatitis patients and healthy subjects. *Arch Dermatol Res* 1995; **287**: 572-580.
- Chan LS, Robinson N, Xu L. Expression of interleukin-4 in the epidermis of transgenic mice results in a pruritic inflammatory skin disease: an experimental animal model to study atopic dermatitis. *J Invest Dermatol* 2001; **117**: 977-983.
- Greaves MW, McDonald-Gibson W. Itch: role of prostaglandins. *Br Med J* 1973; **3**: 608-609.

21. Andoh T, Katsube N, Maruyama M, Kuraishi Y. Involvement of leukotriene B(4) in substance P-induced itch-associated response in mice. *J Invest Dermatol* 2001; **117**: 1621-1626.
22. Yosipovitch G, Greaves MW, Schmelz M. Itch- *Lancet* 2003;
23. Twycross R, Greaves MW, Handwerker H, et al. Itch: scratching more than the surface. *Quart J Med.* 2003; **96**: 7-26.
24. Koblenzer CS. Psychologic and psychiatric aspects of itching. In Bernhard JD Itch Mechanisms and Management of Pruritus. McGraw Hill 1994; pp352-365.
25. Yosipovitch G, Greaves MW. Itch definitions, in Itch Basic Mechanisms and Therapy. Eds. Yosipovitch G, Greaves MW, McGlone F, Fleischer AB. Merceel Dekker 2004 pp 1-4.
26. Yosipovitch G, Goon A, Wee J, et al. The prevalence and clinical characteristics of pruritus among patients with extensive psoriasis. *Br. J Dermatol* 2000; **143**: 969-973.
27. Yosipovitch G, Goon A, Wee J et al. Itch characteristics in Chinese patients with atopic dermatitis using a new itch questionnaire for the assessment of pruritus. *Int J Dermatol* 2002; **41**: 212-216
28. Yosipovitch G, Ansari N, Goon A, et al. Clinical Characteristics of pruritus in patients suffering from chronic idiopathic urticaria. *Br J Dermatol* 2002; **147**: 32-36.
29. Yosipovitch G, Pruritus an Update. *Current Probl Dermatol* 2003; **15**: 135-164.
30. Herman LE. Itching in scars, in Itch Mechanisms and Management of Pruritus Ed. Bernhard. J, McGraw Hill, 1994 pp 153-160.
31. Leow YH, Yosipovitch G. Pruritus in lichen simplex chronicus and lichen amyloidosis. in Itch Basic Mechanisms and Therapy. Eds. Yosipovitch G, Greaves MW, Fleischer AB McGlone F. Merceel Dekker 2004; pp255-258.
32. Ganor S, Dollberg L, Amyloidosis of the nipple presenting as pruritus. *Cutis* 1983; **31**: 318.
33. Gorodeski IG, Cordoba, M, Shapira A, et al. Primary localized cutaneous lichen amyloidosis of the vulva. *Int J Dermatol* 1988; **27**: 259 -260.
34. Weyers W, Weyers I, Bonezkowitz M, et al. Lichen amyloidosis: a consequence of scratching. *J Am Acad Dermatol* 1997; **37**: 923- 928.
35. Liddell K. Post-herpetic pruritus. *Br Med J* 1974; 165.
36. Darsow U, Lorenz J, Bromm B, Ring J. Pruritus circumscriptus sine materia: a sequel of postzoster neuralgia. Evaluation by quantitative psychophysical examination and laser-evoked potentials. *Acta Derm Venereol* 1996; **76**: 45-47.
37. Oaklander AL, Cohen SP Raju SVY, Intractable postherpetic itch and cutaneous deafferentation after facial shingles. *Pain* 2002; **96**: 9-12.
38. Oaklander AL, Bowsher D, Galer B et al. Herpes zoster itch: preliminary epidemiologic data. *J Pain.* 2003; **4**: 338-43.
39. Sugeng MW, Yosipovitch G, Leok GC. Postherpetic neuralgia and the dermatologist. *Int J Dermatol* 2001; **40**(1): 6-11.
40. Massey EW, Pleet AB. Localized pruritus- notalgia paresthetica. *Arch Dermatol* 1979; **115**: 982-983.
41. Bernhard JD. Notalgia paresthetica, macular posterior pigmentary incontinence, macular amyloidosis and pruritus. *Acta Derm Venereol* 1997; **77**: 164.
42. Raison-Peyron N, Meunier L, Acevedo M, Meynadier J. Notalgia paresthetica: clinical, physiopathological and therapeutic aspects. A study of 12 cases. *J Europ Acad Dermatol Venerol* 1999; **12**: 215-221.
43. Savk E, Savk O, Bolukbasi O, Culhaci N, Dikcioglu E, Karaman G, Sendur N. Notalgia paresthetica: a study on pathogenesis. *Int J Dermatol* 2000; **39**: 754-759.
44. Eisenberg E, Barmeir E, Bergman R. Notalgia paresthetica associated with nerve root impingement. *J Am Acad Dermatol* 1997; **37**: 998-1000.
45. Wallengren J. Brachioradial pruritus: a recurrent solar dermopathy. *J Am Acad Dermatol* 1998; **39**: 803-6.
46. Fisher DA. Brachioradial pruritus wanted: a sure cause (and cure) for brachioradial pruritus. *Int J Dermatol* 1997; **36**: 817-818.
47. Kavak A, Dosoglu M. Can a spinal tumor be a causative factor of brachioradial pruritus? *J Am Acad Dermatol* 2002; **46**: 437-440.
48. Massey EW, Massey JM. Forearm neuropathy and pruritus. *South Med J* 1986; **79**(10): 1259-60.
49. Goodkin R, Wingard E, Bernhard J. Brachioradial pruritus: cervical spine disease and neurogenic/neuropathic pruritus. *J Am Acad Dermatol* 2003; **48**: 521-524.
50. Heyl T. Brachioradial pruritus. *Arch Dermatol* 1983; **119**: 115-116.
51. Cohen AD, Masalha R, Medvedovsky et al. Brachioradial pruritus: a symptom of neuropathy. *J Am Acad Dermatol* 2003; **48**: 825-828.
52. King CA, Huff FJ, Jorizzo JL. Unilateral neurogenic pruritus: paroxysmal itching associated with central nervous system lesions. *Ann Intern Med* 1982; **97**(2): 222-223.
53. Shapiro PE, Braun CW. Unilateral pruritus after a stroke. *Arch Dermatol* 1987; **123**: 1527-1530.
54. Massey EW. Unilateral neurogenic pruritus following stroke. *Stroke* 1984; **15**: 901-3.
55. Andreev VC, Petkov I. Skin manifestations associated with tumours of the brain. *Br J Dermatol* 1975; **92**: 675-678.
56. Sullivan MJ, Drake ME. Unilateral pruritus and Nocardia brain abscess. *Neurology* 1984; **34**: 828-829.
57. Shabtai H, Nispeanu P, Chapman J, and Korczyn AD. Pruritus in Creutzfeldt-Jacob disease. *Neurology* 1996; **46**: 940-941.
58. Summers GC, MacDonald JT. Paroxysmal facial itch: a presenting sign of childhood brainstem glioma. *J Child Neurol* 1988; **3**: 189-92.
59. Yamamoto M, Yabuki S, Hayabara T. Paroxysmal itch-

- ing in multiple sclerosis: a report of three cases. *J Neurol, Neurosurg Psychiatry* 1981; **44**: 19-22.
60. Sandyk R. Paroxysmal itching in multiple sclerosis during treatment with external magnetic fields. *Int J Neurosci* 1994; **75**: 65-71.
 61. Darsow U, Scharein E, Simon D, et al. New aspects of itch pathophysiology: component analysis of atopic itch using the 'Eppendorf Itch Questionnaire'. *Int Arch Allergy Immunol* 2001; **124**: 326-331.
 62. Yosipovitch G, Zucker I, Boner G, et al. A questionnaire for the assessment of pruritus: validation in uremic patients. *Acta Derm Venereol* 2001; **81**: 108-111.
 63. Yosipovitch G. Itch Questionnaires as tools for itch evaluation. In: *Itch Basic Mechanisms and Therapy*. Eds. Yosipovitch G, Greaves MW, Fleischer AB, McGlone F. *Mercel Dekker* 2004; pp169-182.
 64. Ebata T, Aizawa H, Kamide R. An infrared video camera system to observe nocturnal scratching in atopic dermatitis patients. *J Dermatol* 1996; **23**: 153-155.
 65. Talbot TL, Schmitt JM, Bergasa NV, et al. Application of piezo film technology for the quantitative assessment of pruritus. *Biomed Instrum Technol* 1991; **25**: 400-403.
 66. Ebata T, Iwasaki S, Kamide R, Niimura M. Use of a wrist activity monitor for the measurement of nocturnal scratching in patients with atopic dermatitis. *Br J Dermatol* 2001; **144**: 305-309.
 67. Bender BG, Leung SB, Leung DY. Actigraphy assessment of sleep disturbance in patients with atopic dermatitis: an objective life quality measure. *J Allergy Clin Immunol* 2003; **111**: 598-602.
 68. Wahlgren CF. Measurement of itch. *Semin Dermatol* 1995; **14**: 277-284.
 69. Yosipovitch G, David M. The diagnostic and therapeutic approach to idiopathic generalized pruritus. *Int J Dermatol* 1999; **38**: 881-887.
 70. Freitag G, Hoppner T. Results of a postmarketing drug monitoring survey with a polidocanol-urea preparation for dry, itching skin. *Curr Med Res Opin* 1997; **13**: 529-537.
 71. Chamlin SL, Kao J, Frieden I, et al. Ceramide-dominant barrier repair lipids alleviate childhood atopic dermatitis: Changes in barrier function provide a sensitive indicator of disease activity. *J Am Acad Dermatol* 2002; **47**: 198-208.
 72. Yosipovitch G, Szolar C, Hui XY, Maibach H. Effect of topically applied menthol on thermal, pain and itch sensations and biophysical properties of the skin. *Arch Dermatol Res* 1996; **288**: 245-248.
 73. Bromm B, Scharein E, Darsow U, Ring J. Effects of menthol and cold on histamine-induced itch and skin reactions in man. *Neurosci Lett* 1995; **187**: 157-160.
 74. Yosipovitch G, Maibach HI. Effect of topical pramoxine on experimentally induced pruritus in humans. *J Am Acad Dermatol* 1997; **37**: 278-80.
 75. Shuttleworth D, Hill S, Marks R, Connelly DM. Relief of experimentally induced pruritus with a novel eutectic mixture of local anaesthetic agents. *Br J Dermatol* 1988; **119**: 535-540.
 76. Drake LA, Fallon JD, Sober A. Relief of pruritus in patients with atopic dermatitis after treatment with topical doxepin cream. *J Amer Acad Dermatol* 1994; **31**: 613-616.
 77. Shelley WB, Shelley ED, Talanin NY. Self potentiating allergic contact dermatitis caused by doxepin hydrochloride cream. *J Am Acad Dermatol* 1996; **34**: 143-144.
 78. Stander S, Metze D. Treatment of pruritic skin diseases with topical capsaicin. In: *Itch Basic Mechanisms and Therapy*. Eds. Yosipovitch G, Greaves MW, Fleischer AB, McGlone F. *Mercel Dekker* 2004; 287-304.
 79. Yosipovitch G, Maibach HI, Rowbotham MC. Effect of EMLA pre-treatment on capsaicin-induced burning and hyperalgesia. *Acta Derm Venereol* 1999; **79**: 118-121.
 80. Cheer SM, Plosker GL. Tacrolimus ointment. A review of its therapeutic potential as a topical therapy in atopic dermatitis. *Am J Clin Dermatol* 2001; **2**(6): 389-406.
 81. Wellington K, Jarvis B. Topical pimecrolimus: a review of its clinical potential in the management of atopic dermatitis. *Drugs* 2002; **62**: 817-840.
 82. Fleischer AB. Treatment of atopic dermatitis: role of tacrolimus ointment as a topical noncorticosteroidal therapy. *J Allergy Clin Immunol* 1999; **104**: 126-130.
 83. Fleischer AB. Reduction in itch severity with topical immunomodulators: a new approach for patients with inflammatory disease. In: *Itch Basic Mechanisms and Therapy*. Eds. Yosipovitch G, Greaves MW, Fleischer AB, McGlone F. *Mercel Dekker* 2004; 315-323.
 84. Daly BM, Shuster S. Effect of aspirin on pruritus. *Br Med J* 1986; **293**: 907.
 85. Yosipovitch G, Ademola J, Ping L, et al. Topically applied aspirin rapidly decreases histamine induced itch. *Acta Derm Venereol* 1997; **77**: 46-48.
 86. Yosipovitch G, Sugeng MW, Chan YH, et al. The effect of topically applied aspirin on localized circumscribed neurodermatitis. *J Am Acad Dermatol* 2001; **45**: 910-913.
 87. Miller MJ, Rueter BK, Wallace JL. Et al. Mechanistic and clinical assessment of Zangrado, an extract of the Amazonian ethnomedicine Sangre de Grado for the treatment of itch. In: *Itch Basic Mechanisms and Therapy*. Eds. Yosipovitch G, Greaves MW, Fleischer AB, McGlone F. *Mercel Dekker* 2004; 305-314.
 88. Zhai H, Hannon W, Hahn GS. Et al. Strontium nitrate decreased histamine - induced itch magnitude and duration in man. *Dermatology* 2000; **200**: 244-246.
 89. Lebwohl M. Phototherapy of pruritus, in Bernhard JD ed. *Itch: Mechanisms and Management of Pruritus*. New York: McGraw- Hill 1994; 399-411.
 90. Krause L, Shuster S. mechanisms of action of antipruritic drugs. *Br Med J* 1983; **287**: 1199-1200.
 91. Monroe E. Desloratdine for the treatment of chronic urticaria. *Skin Therapy Lett* 2002; **7**: 1-5.
 92. Moraes M, Russo G. Thalidomide and its dermatologic uses. *Am J Med Sci* 2001; **321**: 321-326.
 93. Daly BM, Shuster S. Antipruritic action of thalidomide. *Acta Derm Venereol* 2000; **80**: 24-25.
 94. Goodless DR, Eaglstein WH. Brachioradial pruritus: treat-

- ment with topical capsaicin. *J Am Acad Dermatol* 1993; **29**: 783-784.
95. Knight TE, Hayashi T. Solar (brachioradial) pruritus-response to capsaicin cream. *Int J Dermatol* 1994; **33**(3): 206-209.
 96. Bueller HA, Bernhard JB, Dubroff LM. Gabapentin treatment for brachioradial pruritus. *J Europ Acad Dermatol Venerol* 1999; **13**: 227-230.
 97. Rongioletti F. Pruritus as a presenting sign of cervical rib. *Lancet* 1992; **339**: 55.
 98. Goulden V, Toomey PJ, Highet AS. Successful treatment of notalgia paresthetica with a paravertebral local anesthetic block. *J Am Acad Dermatol* 1998; **38**: 114-116.
 99. Layton AM, Cotterill JA. Notalgia Paresthetica - report of three cases and their treatment. *Clin Exp Dermatol* 1991; **16**: 197-8.
 100. Wallengren J. Treatment of notalgia paresthetica with topical capsaicin. *J Am Acad Dermatol* 1991; **24**: 286-288.
 101. Sandroni P. Central neuropathic itch: a new treatment option? *Neurology* 2002; **59**: 778-780.
 102. Sonja Ständer and Dieter Metze Treatment of pruritus in internal and dermatological diseases with opioid receptor antagonists in Itch Basic Mechanisms and Therapy. Eds Yosipovitch G, Greaves MW, Fleischer AB McGlone F. *Mercel Dekker* 2004; 259-278.
 103. Metze D, Reimann S, Beissert S, Luger T. Efficacy and safety of naltrexone, an oral opiate receptor antagonist, in the treatment of pruritus in internal disease and dermatological diseases. *J Am Acad Dermatol* 1999; **41**: 533-539.
 104. Peer G, Kivity S, Agami O et al. Randomised crossover trial of naltrexone in uraemic pruritus. *Lancet* 1996; **348**: 1552-1554.
 105. Pauli-Magnus C, Mikus G, Alschner DM, et al. Naltrexone does not relieve uremic pruritus: results of randomized, placebo controlled crossover- study. *J Am Soc Nephrol* 2000; **11**: 514-519.
 106. 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.
 107. Kumagai H, Maruyama S, Gejyo et al. Role of mu and kappa-opioid systems in systemic and peripheral itch, and effects of a novel kappa-agonist TRK 820. In 2nd International Workshop for the Study of Itch Toyoma Japan pp23-24.
 108. Carey JB. Lowering of serum bile acid concentrations and relief of pruritus in jaundiced patients fed a bile acid sequestering resin. *J Lab Clin Med* 1960; **56**: 797-798.
 109. Silverberg DS, Iaina A, Resin E et al. Cholestyramine in uraemic pruritus. *Br Med J*. 1977; **19**: 752-753.
 110. Ghent CN, Carruthers SG. Treatment of pruritus in primary biliary cirrhosis with rifampin. Results of a double-blind, crossover, randomized trial. *Gastroenterology* 1988; **94**(2): 488-493.
 111. Bachs L, Pares A, Elena M, Piera C, Rodes J. Comparison of rifampicin with phenobarbitone for treatment of pruritus in biliary cirrhosis. *Lancet* 1989; **1**(8638): 574-576.
 112. Nilsson HJ, Levinsson A, Schouenborg J. Cutaneous field stimulation (CFS): a new powerful method to combat itch. *Pain* 1997; **71**: 49-55.
 113. Wallengren J, Sundler F. Cutaneous field stimulation in the treatment of severe itch. *Arch Dermatol* 2001; **137**: 1323-1325.
 114. Gupta MA, Gupta AK. The use of antidepressant drugs in dermatology. *JEADV* 2001; **15**: 512-518.
 115. Koo J, Lee CS. Delusions of parasitosis. A dermatologist's guide to diagnosis and treatment. *Am J Clin Dermatol* 2001; **2**: 285-290.