EDF-Guidelines for Chronic Pruritus

In cooperation with the European Academy of Dermatology and Venereology (EADV) and the Union Européenne des Médecins Spécialistes (UEMS)

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Abbreviations and Explanations

AD	Atopic Dermatitis
AEP	Atopic eruption of pregnancy
CGRP	Calcitonin gene-related peptide
CKD	Chronic kidney disease
CP	Chronic pruritus (longer than 6 weeks)
DIF	Direct immunofluorescence
ICP	Intrahepatic cholestasis of pregnancy
IFSI	International Forum on the Study of Itch
IIF	Indirect immunofluorescence
IL	Interleukin
Itch	Synonymous with pruritus
NSAID	Non-steroidal anti-inflammatory drugs
PAR	Proteinase-activated receptor
PBC	Primary biliary cirrhosis
PEP	Polymorphic eruption of pregnancy
PG	Pemphigoid gestationis
PN	Prurigo nodularis
Pruritus	A skin sensation which elicits the urge to scratch
PUO	Pruritus of unknown origin
PTH	Parathyroid hormone
PV	Polycythaemia vera
RCT	Randomized controlled trials
SSRI	Selective serotonin re-uptake inhibitors
TRP	Transient receptor potential
UV	Ultraviolet
VIP	Vasoactive intestinal peptide

1 The challenge of writing these guidelines 4
2 Definitions and clinical classification 4
3. Diagnostic management 5
3.1 Patient's history, examination and clinical characteristics of pruritus 5
3.2 Diagnostic algorithm and Diagnostics 7
4. Therapy 7
4.1 Therapy: General principles 7
4.2 Causative therapy and etiology specific treatment 8
4.3. Symptomatic therapy: topical 8
4.3.1 Local anaesthetics 8
4.3.2 Glucocorticosteroids 9
4.3.3. Capsaicin 9
4.3.4. Cannabinoid agonists 10
4.3.5 Tacrolimus and Pimecrolimus 11
4.3.6 Acetylsalicylic Acid 11
4.3.7 Doxepin 12
4.3.8 Zinc, Menthol and Camphor 12
4.3.9 Mast cell inhibitors 12
4.4 Systemic Therapy 13
4.4.1 Antihistamines 13
4.4.2 Mast cell inhibitors 14
4.4.3 Glucocorticosteroids 15
4.4.5 Opioid receptor antagonists 15
4.4.6 Gabapentin 16
4.4.7 Antidepressants 16
4.4.8 Serotonin receptor antagonists 17
4.4.9 Thalidomide 18
4.4.10 Ciclosporin A 18
4.5 UV Phototherapy 19
4.6 Psychosomatic therapy (Relaxation techniques and Psychotherapy) 21
5. References 33

1 The challenge of writing these guidelines

Chronic pruritus (CP) is a frequent symptom in the general population and in many skin and systemic diseases (Weisshaar, Dalgard 2009). Its frequency demonstrates a high burden and an impaired quality of life. These guidelines address a symptom and not a disease. As a consequence of the diversity of possible underlying diseases, no single therapy concept can be recommended. Each form of pruritus has to be considered individually. To date, there is still a significant lack of randomized controlled trials (RCT), which can be explained by the diversity and complexity of this symptom, multifactorial aetiologies of pruritus and the lack of well-defined outcome measures. To complicate matters, RCT exist for some types of pruritus, but with conflicting results. However, new therapies for improved medical care have been suggested.

The health care system in many countries and their social economic situation with constantly reducing financial resources increases the need for guidelines. These expert recommendations are based on a consensus of participating countries, while also allowing for country-specific treatment modalities and health care structures. Furthermore, it should be appreciated that some topical and systemic therapies can only be prescribed “off-label” and require informed consent. If such “off-label” therapies cannot be initiated in the physician’s office, cooperation with a specialised centre for pruritus might be helpful.

These guidelines address all medical disciplines that work with patients suffering from CP. They are not only focused on dermatology.

2 Definitions and clinical classification

The definitions presented in these guidelines are based on a consensus among the European participants; however some of them have provoked controversy. Most of the contributors accept pruritus and itch to be synonymous. Following the International Forum on the Study of Itch (IFSI), the term “pruritus sine materia” will not be used in this guideline (Ständer, Weisshaar et al. 2006). In patients with no identified underlying disease, the term “pruritus of unknown origin” or “pruritus of

undetermined origin" (PUO) is used. The term "pruritus of unknown etiology" should be avoided as in most clinically well-defined forms of pruritus the mechanism is unknown (e.g. chronic kidney disease (CKD) associated pruritus). A practical distinction is that between acute pruritus and chronic forms (lasting six weeks or longer). Pruritus / itch is a sensation that provokes the desire to scratch. These guidelines address patients presenting with CP of different including unknown origin. If the underlying cause is detected, disease-specific guidelines should be consulted (e.g. atopic dermatitis (AD), cholestatic pruritus) (Darsow, Lubbe et al. 2005; Misery 2005; Misery, Alexandre et al. 2007; Magerl, Borzova et al. 2009).

According to the IFSI classification, the aetiology of CP is classified as I "dermatological", II "systemic", III "neurological", IV "somatoform", V "mixed origin" and VI "others" (Ständer S, Weisshaar E et al 2007). The IFSI classification comprises a clinical distinction of patients with I pruritus on primarily inflamed skin, II pruritus on normal skin and III pruritus with chronic secondary sratch lesions.

Somatoform pruritus is defined as pruritus where psychiatric and psychosomatic factors play a critical role in the initiation, intensity, aggravation or persistence of the pruritus. It is best diagnosed using positive and negative diagnostic criteria (Misery, Alexandre et al. 2007).

3. Diagnostic management

3.1 Patient's history, examination and clinical characteristics of pruritus

The patient's history and clinical examination are crucial when they present with CP, as it is an assessment of their pruritus including intensity, onset, time course, quality, localisation, triggering factors and the patient's theory of causality. Attention should be paid to incidents preceding or accompanying the onset of pruritus (e.g. pruritus following bathing). It is also important to consider the methods used to relieve pruritus, e.g. brushes. This helps with the interpretation of clinical findings such as the absence of secondary skin lesions in the mid-back known as the "butterfly sign" which indicates that the patient cannot reach this area by hand and is thus unable to scratch it. It is also important to ask about preexisting diseases, allergies, atopic diathesis and drug intake (table 1). A great deal of helpful information can be obtained using questionnaires. There are no definite clinical findings related to specific pruritic diseases (Weisshaar,

Apfelbacher et al. 2006), but awareness of the following anamnestic aspects and clinical findings may help with the diagnosis of the cause of pruritus:

- When several family members are affected, scabies or other parasites should be considered.
- The relationship between pruritus and special activities is important: Pruritus during physical activity is suggestive of cholinergic pruritus. It is common in patients with atopic eczema and mild forms of cholinergic pruritus. Pruritus provoked by skin cooling after bathing should prompt consideration of aquagenic pruritus. It may be associated or precede lymphoma or PV, and screening for these diseases should be performed intermittently.
- Nocturnal generalised pruritus associated with chills, fatigue, tiredness and "B" symptoms (weight loss, fever and nocturnal sweating) raises the possibility of Hodgkin's disease.
- Psychogenic pruritus rarely disturbes sleep, most other pruritic diseases cause nocturnal wakening.
- Seasonal pruritus frequently presents as "winter itch", which may also be the manifestation of pruritus in the elderly due to xerosis cutis and asteatotic eczema.

A patient's history should always include all current and recent medications, infusions and blood transfusions. Severe pruritus can lead to considerable psychological distress. This should not be underestimated by the physician and should be addressed directly. CP can be accompanied by behavioural/adjustment disorder and a withdrawal from social and work life (Schneider, Driesch et al. 2006). In these cases, psychosomatic counselling is required. CP with excoriations sometimes progressing to self-mutilation can be caused by psychiatric disease such as delusional parasitosis. Such patients need psychiatric examination and if necessary treatment. A solely psychological cause of pruritus should not be diagnosed without psychiatric examination.

Examination of patients with CP includes a thorough inspection of the entire skin including mucous membranes, scalp, hair, nails and anogenital region. The distribution of primary and secondary skin lesions should be recorded together

with skin signs of systemic disease. General physical examination should include palpation of the liver, kidneys, spleen and lymph nodes.

There is no standardised method of documenting pruritus. The sensation of pruritus is subject to much inter- and intra-individual variation due to tiredness, anxiety, stress. The intensity of pruritus can be assessed using a questionnaire or a visual analogue scale (VAS). When using a VAS, the scale ranges from 0 – 10 and is graphically presented as a bar chart. However, these methods often fail to consider the frequency of itch attacks over the course of a day. For patients with severe PUO, it can be helpful to keep a diary in order to allow for clearer attribution of the symptoms.

3.2 Diagnostic algorithm and Diagnostics

Laboratory screening, clinical and technical approaches and investigations are summarised in Table 1 and Table 2. All this helps to follow a diagnostic algorithm (Table 3).

4. Therapy

4.1 Therapy: General principles

In the patient with CP it is important to establish their age, pre-existing diseases, medications, quality and intensity of pruritus and accordingly plan an individual therapy regimen. Most importantly, elderly, pregnant women and children need special attention. As the care of patients with CP often extends over a long period, with initial uncertainty about the origin of their pruritus, frustration regarding the failure of past therapies and general psychological stress frequently occurs. The diagnostic procedures and therapy should be discussed with the patient in order to achieve best possible concordance. It must be remembered that some therapies are not licensed for CP and can only be prescribed “off-label”. This requires separate informed consent.

First, the patient should be informed about general pruritus-relieving measures (Table 4). They include simple and helpful measures such as wet and cold wraps,

application of lotio alba etc. Prior to further symptomatic therapy, the patient should be subject to a careful diagnostic evaluation and therapy given for any underlying disease (Tables 2, 3). If pruritus still persists, combined or consecutive step-by-step symptomatic treatment is necessary (Table 10). Specific pharmacological interventions should be performed according to the guideline of the specific disease and the field's Cochrane Group (Zuberbier, Bindslev-Jensen et al. 2005; EASL 2009).

4.2 Causative therapy and etiology specific treatment

Pruritus can be addressed by treating the underlying disease. Therapeutic measures include specific treatments of underlying dermatoses, avoidance of contact allergens, discontinuation of implicated drugs, specific internal, neurological and psychiatric therapies, surgical treatment of an underlying tumour or transplantation of organs. Normally there is sudden relief of pruritus when the underlying disease improves, e.g. when Hodgkin's disease responds to chemotherapy or when a patient with CKD-associated pruritus has been transplanted. For some underlying diseases specific treatments have proven to be successful in relieving pruritus, even if the underlying disease is not treated. Etiology specific treatments act on a known or hypothetically assumed pathogenesis of pruritus in underlying diseases. For only a few of these treatments evidence of efficacy can be found in RCT. Treatments for CP in specific diseases are presented in Tables 5-9. When deciding the choice of treatment, consideration should be given to the level of evidence, side-effects, practicability, costs, availability of a treatment and individual factors such as patient's age.

4.3. Symptomatic therapy: topical

4.3.1 Local anaesthetics

Local anaesthetics act via different groups of skin receptors. They can be used for pain, dysaesthesia and pruritus. Benzocaine, lidocaine, pramoxine as well as a mixture of prilocaine and lidocaine are widely used topically, but only have a short-term effect. In experimental studies, the antipruritic effect of local anaesthetics is limited in diseased skin e.g. AD (Weisshaar, Heyer et al. 1996; Weisshaar, Forster et al. 1997). Successful application in the treatment of localised forms of pruritus

such as notalgia paraesthetica has been reported (Layton and Cotterill 1991; Weisshaar, Heyer et al. 1996). When treating larger skin areas, polidocanol 2-10% in different galenic formulations can be used, frequently in combination with 3% urea. There are no controlled clinical trials investigating the antipruritic effects of local anaesthetics.

Expert recommendation: Short term application of topical local anaesthetics can be recommended as an additional therapy. The risk of sensitization can be considered as low.

4.3.2 Glucocorticosteroids

Pruritus experimentally induced by histamine was significantly suppressed by topical hydrocortisone when compared to placebo (Zhai et al. 2000). All other clinical studies apply to an underlying inflammatory dermatosis in which ”pruritus” was one parameter among many. Clinical experience shows that topical glucocorticosteroids can be effective if itch is the consequence of an inflammatory dermatosis. Use of topical glucocorticosteroids to treat the symptom of pruritus is not advised in the absence of an inflammatory dermatosis. Topical glucocorticosteroids with a favourable side-effect profile (e.g. fluticasonpropionate, methylprednisolon-aceponate or mometasonfuorate) are to be preferred (Al-Ghnaniem, Short et al. 2007; Szczepanowska, Reich et al. 2008). In some cases the anti-inflammatory effect of glucocorticosteroids is helpful, but insufficient to completely abolish pruritus (Kawashima et al. 2003).

Expert recommendation: Initial short-term application of topical glucocorticosteroids can be recommended in CP associated with an inflammatory dermatosis, but should not be used as long-term treatment or in the absence of a primary rash.

4.3.3. Capsaicin

Capsaicin (trans-8-metyl-N-vanillyl-6-nonenamide) is the pungent agent of chilli peppers and is used as a pain-relieving medication (Szolcsanyi 2004). Topical application of capsaicin activates sensory C-fibres to release neurotransmitters inducing dose-dependent erythema and burning. After repeated applications of capsaicin, the burning fades due to tachyphylaxis (Szolcsanyi 2004). However,

pruritus reoccurs some weeks after discontinuation of therapy indicating no permanent degeneration of the nerve fibers (Wallengren und Hakanson 1992).
The greater the initial dose of capsaicin and the more frequent the applications, the sooner the desensitization will appear and itch disappear. Severe initial burning may be a side-effect of topical application. Cooling of the skin can also reduce the capsaicin-evoked burning. The concentration of capsaicin varies in different studies, but 0.025% capsaicin is tolerated well by most patients. If capsaicin is not available in this concentration as a standard drug it can be made using a lipophilic vehicle. It is also well soluble in alcohol; capsaicin 0.025% in *spir dil* can be used to treat itchy scalp (not published). A weaker concentration of 0.006% capsaicin in ung Merck is recommended for intertriginous skin e.g. pruritus ani (Lysy, Sistiery-Ittah et al. 2003).
Topical capsaicin's effects have been confirmed in RCT for different pain syndromes and neuropathy as well as notalgia paraesthetica (Wallengren and Klinker 1995), brachioradial pruritus (Wallengren 1998), pruritic psoriasis (Bernstein, Parish et al. 1986; Ellis, Berberian et al. 1993) and haemodialysis-related pruritus (Breneman, Cardone et al. 1992; Tarng, Cho et al. 1996). Case reports and case series described effects in hydroxyethyl starch-induced pruritus (Szeimies, Kueffer et al. 1998; Reimann, Luger et al. 2000), prurigo nodularis (Hoogenberg, Tupker et al. 1992; Tupker, Coenraads et al. 1992; Reimann, Luger et al. 2000; Stander, Luger et al. 2001), lichen simplex (Tupker, Coenraads et al. 1992; Reimann, Luger et al. 2000), nummular eczema (Reimann, Luger et al. 2000), aquagenic pruritus (Lotti, Teofoli et al. 1994) and PUVA-associated pruritus (Kirby and Rogers 1997).
Expert recommendation: Capsaicin can be effective in localized forms of CP, but patient compliance due to side-effects can restrict usage.

4.3.4. Cannabinoid agonists

Topical cannabinoid agonists are a new development since 2003 and appear to have antipruritic and analgesic properties. Experimentally induced pain, itch and erythema could be reduced by application of a topical cannabinoid agonist (Dvorak, Watkinson et al. 2003; Rukwied, Watkinson et al. 2003). One cosmetic product containing the cannabinoid agonist N-palmitoylethanolamin is currently on the market. In clinical trials and case series, it proved to have antipruritic effects in

prurigo, AD, CKD-associated pruritus and PUO (Szepietowski, Szepietowski et al. 2005; Stander, Reinhardt et al. 2006; Eberlein, Eicke et al. 2008).

Expert recommendation: Cannabinoid agonists can be effective in the treatment of localized pruritus.

4.3.5 Tacrolimus and Pimecrolimus

The effects of tacrolimus and pimecrolimus on pruritus are mediated both through their immunological and neuronal properties (Stander and Luger 2003). Paradoxically, while they can induce transient itch at the beginning of treatment, in the medium-term they may provide an alternative treatment for many causes of pruritus. They are very effective against pruritus in AD. Clinical trials have shown benefit in contact and seborrhoeic dermatitis, genital lichen sclerosus, intertriginous psoriasis and cutaneous lupus erythematosus (Simpson and Noble 2005; Wollina, Hansel et al. 2006). In other diseases, the available data are limited to small case series, or individual cases e.g. graft-versus-host disease, vulval pruritus or Netherton's syndrome. Topical tacrolimus has also been shown anecdotally to be effective in itch associated with systemic diseases such as primary biliary cirrhosis (PBC) (Aguilar-Bernier, Bassas-Vila et al. 2005) and CKD (Pauli-Magnus, Klumpp et al. 2000; Kuypers, Claes et al. 2004), however these observations have not been confirmed in RTCs on CKD-associated pruritus (Duque, Yosipovitch et al. 2005). Both substances can be used to treat localised forms of CP such as genital pruritus (Stander, Schuermeyer-Horst et al. 2006).

Expert recommendation: Tacrolimus and pimecrolimus are effective in localised forms of CP.

4.3.6 Acetylsalicylic Acid

Topical acetylsalicylic acid (acetylsalicylic acid/dichlormethane solution) has been described to have antipruritic effects in occasional patients with lichen simplex (Yosipovitch, Sugeng et al. 2001). However, this beneficial effect could not be confirmed in experimentally induced itch with histamine (Thomsen, Benfeldt et al. 2002).

Expert recommendation: Due to the lack of studies, topical acetylsalicylic acid can currently not be recommended for CP.

4.3.7 Doxepin

The tricyclic antidepressant doxepin showed antipruritic effects when applied as a 5% cream in double-blind studies for treatment of AD (Drake, Fallon et al. 1994), lichen simplex, nummular dermatitis and contact dermatitis (Drake and Millikan 1995). Topical doxepin therapy is not licensed and not used in any European country except for the UK (Xepin©) (Greenberg 1995; Shelley, Shelley et al. 1996; Bonnel, La Grenade et al. 2003).

Expert recommendation: Due to an increased risk of contact allergy, especially when the treatment exceeds eight days, topical doxepin cannot be recommended.

4.3.8 Zinc, Menthol and Camphor

Although zinc oxide has been used in dermatology for over 100 years due to its anti-inflammatory, antiseptic and anti-pruritic properties and its safety, there is only scarce literature on its effects. *Ex tempore* prescriptions of zinc are frequent, with concentrations varying from 10 to 50% in creams, liniments, lotions, ointments and pastes that are useful in the treatment of pruritus, especially for localised forms of pruritus, in children as well as in adults (Welsh 1955).

Menthol is an alcohol obtained from mint oils, or prepared synthetically. It is used in dusting powders, liniments, lotions and ointments in concentrations from one to 10% (Welsh 1955). Short-term application of such medications in CP in combination with other topical or systemic therapies can be recommended.

Camphor is an essential oil containing terpenes, it is soluble in alcohol (Welsh 1955). It has been used in dermatology for decades in liniments, lotions and ointments in concentrations from 2-20%.

Expert recommendation: Short term application of camphor, menthol and zinc in combination with other topical or systemic therapies can be recommended.

4.3.9 Mast cell inhibitors

In a multi-center, double-blind, placebo-controlled trial, application of a 3% hydrogel formulation of tiacrilast against vehicle in AD let to know significant improvement of CP (Czarnetzki, Brechtel et al. 1993).

Pruritus in AD responds to topical sodium cromoglycate (Haider 1977), which was proved by a recent placebo-controlled study (Stainer, Matthews et al. 2005).

Expert recommendation: There is limited evidence to recommend the systemic use of topical mast cell inhibitors for CP.

4.4 Systemic Therapy

4.4.1 Antihistamines

Antihistamines are the most widely used systemic antipruritic drugs in dermatology. Most antihistamines that have been tried in pruritus belong to the H1 type. First generation antihistamines, such as chlorpheniramine, clemastine, cyproheptadine, diphenhydramine, hydroxyzine, and promethazine are known to bind not only to H1-receptors but also to muscarinic, α-adrenergic, dopamine or serotonin receptors and have a central sedative effect. Due to side effects, the application of sedative antihistamines is nowadays limited. Second generation antihistamines like cetirizine, levoceterizine, desloratadine, ebastine, fexofenadine and loratadine have minimal activity on non-histaminic receptors, little sedative effect, and a longer duration of action compared to the first generation (O'Donoghue and Tharp 2005). Non-sedative H1-receptor antagonists offer an effective reduction of itch in diseases associated with increased mast cell degranulation like urticaria or mastocytosis (O'Donoghue and Tharp 2005). However, the doses required to alleviate pruritus in urticaria often amount to two to three times the licensed dose (Asero 2007). Higher doses of the second generation antihistamines enhance their soporific side effects (O'Donoghue and Tharp 2005), which may contribute to their efficacy. Systemic H1-antihistamines are often employed to combat itch in AD, but only sedative antihistamines have shown some benefit, mainly by improving sleep (Hoare, Li Wan Po et al. 2000). Hydroxyzine is the most commonly used antihistaminic of the first generation showing sedative, anxiolytic and antipruritic activities. In adult patients, it is recommended as an antipruritic agent in the dosage 75-100 mg/day. In children the effective dose is 1-2.5mg/kg/day. In a controlled study, addition of hydroxyzine resulted in a 750-fold increase in the dose of histamine required to elicit itch. This compared to five-fold increase following both cyproheptadine and placebo and ten-fold increase following diphenhydramine (Rhoades, Leifer et al. 1975). In addition, hydroxyzine was significantly more effective in reducing histamine-induced pruritus

than neuroleptics, like thiothixene, chlorpromazine and thioridazine (Arnold, Simpson et al. 1979).

Antihistamines are widely used as first-line drugs for treatment of pruritus associated with different systemic diseases such as chronic renal failure, cholestasis, hematopoetic diseases and thyroid disorders. However, conventional doses of antihistamines in the treatment of CP in internal diseases have not proven to be effective (O'Donoghue and Tharp 2005).

A combination of H2-antihistamines and H1-antihistamines has been used in treatment of CP in small trials but the results are conflicting (Paul and Bodeker 1986; Hoare, Li Wan Po et al. 2000). A combination of H1-antihistamine with a leukotriene antagonist has been reported to alleviate pruritus in chronic urticaria (Nettis, Colanardi et al. 2004).

Expert recommendation: Antihistamines are effective in treating CP in urticaria. Antihistamines are of some value for itch in AD and CP of diverse origin. As there is limited evidence of antipruritic effects of non-sedating antihistamines in AD, polycythemia vera (PV) and CP of diverse origin, sedating antihistamines can be recommended to be applied during night time for sleep improvement. Hydroxyzine is the first choice of the majority of physicians trying to control CP but its sedative effect may contraindicate its use in the elderly.

4.4.2 Mast cell inhibitors

Ketotifen, a mast cell stabilizer, showed antipruritic effects in single investigated patients with CKD-associated pruritus (Francos, Kauh et al. 1991). Two patients with CKD-associated pruritus (Rosner 2006) and Hodgkin´s lymphoma (Leven, Naysmith et al. 1977) showed significant lessening of pruritus severity upon treatment with the mast cell stabilizer cromolyn sodium. Also pruritus in AD responds to topical sodium cromoglycate (Haider 1977), which was proved by a recent placebo-controlled study (Stainer, Matthews et al. 2005).

Expert recommendation: There is insufficient evidence to recommend the systemic use of mast cell inhibitors for pruritus.

4.4.3 Glucocorticosteroids

There are no studies investigating the efficacy of the exclusive use of systemic glucocorticosteroids in pruritus. In clinical experience, pruritus ceases within approximately 30 minutes of i.v. glucocorticosteroids in the treatment of urticaria or drug-induced exanthema. Likewise, in AD, allergic contact dermatitis, dyshidrosis and bullous pemphigoid, rapid reduction of pruritus is observed, which can be explained by the high anti-inflammatory potency of glucocorticosteroids. Thus, while systemic glucocorticosteroids should not be considered as an antipruritic for long-term therapy, short-term use is possible in cases of severe pruritus, but should not be prescribed for a period of more than two weeks (Streit, Von Felbert et al. 2002) because of severe side-effects.

Prednisone is the most commonly selected oral corticosteroid initially at a daily dose which can range from 2.5 mg to 100 mg daily or more, usually starting in a dose of 30-40 mg daily. In exceptional cases, i.v.methylprednisolone is used at a dose of 500 mg to 1 g per day, because of its high potency and low sodium-retaining activity. It is important to remember that the dosage should be tapered in accordance with the severity of pruritus. Before discontinuing systemic therapy one may change to topical corticosteroid therapy. Corticosteroids should be used with caution in children and the elderly as well as in patients with relevant metabolic disorders such as diabetes.

Expert recommendation: Systemic corticosteroids can be used as short-term treatment in severe cases of CP, but should not be used for longer than 2 weeks.

4.4.5 Opioid receptor antagonists

Experimental and clinical observations have demonstrated that pruritus can be evoked or intensified by endogenous or exogenous opioids (Fjellner and Hagermark 1982). This phenomenon can be explained by activation of spinal opioid receptors, mainly μ-opioid receptors. Reversing this effect with μ-opioid antagonists thus leads to an inhibition of pruritus.

Several clinical studies have demonstrated different μ-opioid receptor antagonists may significantly diminish CP (Bergasa, Talbot et al. 1992; Bergasa, Alling et al. 1995; Wolfhagen, Sternieri et al. 1997; Bergasa, Schmitt et al. 1998; Bergasa, Alling et al. 1999; Bergasa 2005; Phan, Bernhard et al. 2010). In double-blind RCT, μ-opioid receptor antagonists such as nalmefine, naloxone and naltrexone

have exhibited high antipruritic potency. For example, pruritus in chronic urticaria, AD, and cholestatic pruritus has shown therapeutic response to nalmefene (10 mg twice daily) and naltrexone (50 - 100 mg /day) (Banerji, Fox et al. 1988; Monroe 1989). Controlled studies have also been performed in patients with CKD-associated pruritus (Peer, Kivity et al. 1996; Ghura, Patterson et al. 1998; Pauli-Magnus, Mikus et al. 2000). Results were variable from significant reduction of pruritus to no response. Case reports have demonstrated efficacy in prurigo nodularis, macular amyloidosis, lichen amyloidosis, pruritus in mycosis fungoides, psoriasis vulgaris, aquagenic pruritus, hydroxylethyl starch induced pruritus and PUO.

Expert recommendation: opioid receptor antagonists may be effective in cholestatic pruritus and AD but their side-effect profile needs to be considered.

4.4.6 Gabapentin

Gabapentin is an antiepileptic drug, also used in neuropathic disorders causing pain or pruritus (Misery 2005). The mechanisms of action of gabapentin, a 1-amino-methyl-cyclo-hexane acetic acid and a structural analogue of the inhibitory neurotransmitter γ-aminobutyric acid (GABA), remain unclear. It is used in postherpectic neuralgia (Argoff, Katz et al. 2004), especially when paroxysmal pain or pruritus occurs. Anecdotal indications are brachioradial pruritus (Kanitakis 2006) or cutaneous T-cell lymphoma (Demierre and Taverna 2006). Pilot studies have been performed for the treatment of itching produced by burns and wound healing in children (Mendham 2004). Double-blind RTCs were performed for CKD-associated pruritus (Gunal, Ozalp et al. 2004) and cholestatic pruritus (Bergasa, McGee et al. 2006). Gabapentin was safe and effective for treating CP in haemodialysis patients. Pregabalin is similar to gabapentin and a more recent drug. Its use has been suggested in a case of cetuximab-related itch and aquagenic pruritus (Porzio, Aielli et al. 2006; Ehrchen and Stander 2008).

Expert recommendation: Gabapentin can be recommended in the treatment of CKD-associated pruritus and neuropathic CP.

4.4.7 Antidepressants

Psychoemotional factors are known to modulate the ‘itch threshold.’ Under certain circumstances, they can trigger or enhance CP (Paus, Schmelz et al. 2006). Itch is

a strong stressor and can elicit psychiatric disease and psychological distress. Depressive disorders are present in about 10% of patients with CP (Schneider, Driesch et al. 2006). Consequently, depressive symptoms are treated in these patients and some antidepressants also exert an effect on itch through their pharmacological action on serotonin and histamine. SSRIs, such as paroxetine, can have an antipruritic effect on patients with PV, psychogenic or paraneoplastic pruritus, and other patients with PUO (Zylicz, Krajnik et al. 2003). Tricyclic antidepressants, like mirtazapine (Davis, Frandsen et al. 2003) and especially doxepin (Shohrati, Tajik et al. 2007) have been effective in urticaria, AD and HIV-related pruritus.

The SSRI paroxetine (20 mg/d) has exhibited antipruritic effects in pruritus due to PV (Tefferi and Fonseca 2002), paraneoplastic pruritus (Zylicz, Smits et al. 1998) and psychiatric disease (Biondi, Arcangeli et al. 2000). In two patients, pruritus was induced by discontinuation of paroxetine treatment for depression (Mazzatenta, Peonia et al. 2004). A RCT in pruritus of non-dermatologic origin confirmed the antipruritic effect of paroxetine (Zylicz, Krajnik et al. 2003). In a two-armed proof-of-concept study with paroxetine and fluvoxamine, patients with pruritus of dermatological origin reported significant antipruritic effect (Stander, Bockenholt et al. 2009). As severe cardiac side effects have been described, especially in the elderly this therapy should be used with caution. A psychosomatic/psychiatric examination before starting the treatment is recommended because of its stimulative effects.

Expert recommendation: SSRIs can be recommended for the treatment of somatoform pruritus, paraneoplastic CP, PUO. Mirtazapine can be recommended in CP of AD.

4.4.8 Serotonin receptor antagonists

Due to the pathophysiological significance of serotonin in different diseases such as kidney and liver diseases, serotonin receptor antagonists (of the 5-HT3 type) such as ondansetron (8 mg 1-3x/d), topisetron (5 mg/d) and granisetron (1 mg/d) have been used anecdotally to treat CP (Schworer and Ramadori 1993; Schworer and Ramadori 1993; Raderer, Muller et al. 1994; Andrews, Quan et al. 1995; Schworer, Hartmann et al. 1995; Jones 1999; Albares, Betlloch et al. 2003). Contradictory or negative results have been reported in partly RCT using

ondansetron for cholestatic pruritus (Schworer, Hartmann et al. 1995; O'Donohue, Haigh et al. 1997; Muller, Pongratz et al. 1998) and opioid-induced pruritus (Larijani, Goldberg et al. 1996; Borgeat and Stirnemann 1999; Kjellberg and Tramer 2001). An antipruritic effect was reported for ondansetron in CKD-associated pruritus (Balaskas, Bamihas et al. 1998). However, this could not be confirmed in subsequent RCT (Ashmore, Jones et al. 2000; Murphy, Reaich et al. 2003; Weisshaar, Dunker et al. 2004) later on.

Expert recommendation: Due to the lack of convincing evidence, serotonin receptor antagonists cannot be recommended for the therapy of pruritus.

4.4.9 Thalidomide

A number of mechanisms for the antipruritic action of thalidomide have been proposed including a central depressant effect (Daly and Shuster 2000), a local effect on proliferated neural tissue in PN (van den Broek 1980) and the antagonism of TNFα (Arrese, Dominguez-Soto et al. 2001).

The best results with thalidomide in CP have been achieved in PN. Several studies have shown a rapid decrease of pruritus on thalidomide (50 - 300 mg per day) (Winkelmann, Connolly et al. 1984; Johnke and Zachariae 1993). A prospective open trial of thalidomide 100 mg per day, followed by narrow-band UVB (TL-01) showed a high response with minimal side-effects (Ferrandiz, Carrascosa et al. 1997). Likewise, good results have been seen in HIV-positive patients with PN (Maurer, Poncelet et al. 2004). There is one randomized double-blind cross-over trial of the successful treatment of CKD-associated pruritus with thalidomide (Silva, Viana et al. 1994). Thalidomide is teratogenic and there is a dose-related risk of neuropathy, especially in high daily doses (> 100 mg/d) (Gaspari 2002).

Expert recommendation: Though there is evidence for its antipruritic effect, thalidomide is not recommended for the treatment of CP due to its side effects.

4.4.10 Ciclosporin A

Pruritus in AD responds to treatment with ciclosporin A as demonstrated in double-blind RCT (van Joost, Stolz et al. 1987; Wahlgren, Scheynius et al. 1990). Ciclosporin A has been administered in PN for 24 to 36 weeks, using doses of 3.0-4.5 mg/kg per day. Improvement was observed in both itch and nodularity after

two weeks of treatment (Berth-Jones, Smith et al. 1995; Siepmann, Luger et al. 2008) . It seems likely that in these diseases ciclosporin A acts on pruritus through its immunological effects. However, direct effects on nerve endings are also probable, suggested by successful use in non-immunological diseases as reported in several studies, e. g. ten patients with senescent pruritus were treated with ciclosporin A 5 mg/kg per day for eight weeks (Teofoli, De Pita et al. 1998). All patients of this uncontrolled, open study responded. Case reports describe antipruritic effects in dystrophic epidermolysis bullosa associated CP and in CKD (Calikoglu and Anadolu 2002); (Fusaro, Munaretto et al. 2004).

Expert recommendation: Ciclosporin A can be recommended in CP of AD or PN.

4.5 UV Phototherapy

Ultraviolet (UV)-based therapy is well established for treating pruritus and utilizes UVB (290–320 nm) and UVA (320–400 nm). The light sources include broadband UVB (BB-UVB, 290–320 nm, peaks at 313 nm), narrowband UVB (NB-UVB, 311 nm), broadband UVA (320–400 nm, peaks at 355 nm), and UVA1 (340–400 nm, peaks at 365 nm) (Rivard and Lim 2005).

Inflammatory dermatoses associated with pruritus respond well to different UV-treatments including UVB 311: For the treatment of AD, early studies demonstrated that UVB was better than placebo (Jekler and Larko 1988). In a recent study, NB-UVB was better than BB-UVA and both were better than placebo (Reynolds, Franklin et al. 2001). In the treatment of pruritus of AD, BB-UVB and UVA were equally effective in a half-body comparison (Jekler and Larko 1991). In a more recent study, NB-UVB was insignificantly better than UVA1 for pruritus (Legat, Hofer et al. 2003). In AD, phototherapy seems to act locally rather than systemically: When one half of the body was treated with UVB and the other half was not, only the treated side improved (Jekler and Larko 1988).

For the treatment of prurigo PUVA, UVA1 and NB-UVB proved to be effective in a RCT, with PUVA and UVA1 superior to NB-UVB (Gambichler, Hyun et al. 2006).

For many other skin diseases, a number of studies have demonstrated the efficacy of UV-treatment, e.g. psoriasis, lichen planus, T-cell lymphoma, urticaria, and urticaria pigmentosa.

It can be assumed that in cases of pruritic inflammatory dermatoses pruritus is reduced by inhibiting pro-inflammatory mediators and induction of anti-

inflammatory and immunosuppressive factors. UVB mainly affects epidermal keratinocytes and Langerhans cells, due to its limited penetration into the skin. UVA1, in contrast, reaches to the dermis and therefore can affect T lymphocytes, mast cells, and dermal dendritic cells, e.g. induces apoptosis of these cells (Rivard and Lim 2005). However, UV-B-induced apoptosis of mast cells has been argued to explain relief of pruritus (Szepietowski, Morita et al. 2002). Furthermore phototherapy leads to a reduction of calcitonine gene-related peptide (CGRP) - immunoreactive nerve fibres in the skin (Wallengren and Sundler 2004).

In conditions with CP on primarily non-inflamed skin, UV-therapy has been particularly effective in CKD-associated pruritus (Saltzer and Grove 1975; Gilchrest, Rowe et al. 1977). In a placebo-controlled trial, UVA alone proved ineffective for this condition (Taylor, Taylor et al. 1983). However, an antipruritic effect was seen in CKD-associated pruritus when treated with combined UVA/UVB phototherapy (Berne, Vahlquist et al. 1984). BB-UVB alone was effective in treating CKD-associated pruritus. It was remarkable that in spite of placebo control (only one body half was treated) an improvement of pruritus occurred over the entire body (Gilchrest, Rowe et al. 1979), suggesting a systemic antipruritic effect. In an open pilot study using NB-UVB 14/20 CKD-associated pruritus patients responded well to treatment (Ada, Seckin et al. 2005). Also in a recent study NB-UVB appeared to be effective in reduction of CKD-associated pruritus (Seckin, Demircay et al. 2007). However in another case NB-UVB treatment was unsuccessful, but BB-UVB helped (Hsu and Yang 2003).

UV therapy has also been reported to be effective in a number of cases of metabolic itch. In PV, 8/10 patients responded to NB-UVB in an open study (Baldo, Sammarco et al. 2002). Aquagenic pruritus has shown response to bath PUVA therapy (Jahn, von Kobyletzki et al. 1997) and systemic PUVA (Martinez-Escribano, Quecedo et al. 1997) for the duration of therapy. To treat aquagenic pruritus, PUVA was found to be superior to BB-UVB in 5 patients (Menage, Norris et al. 1993). Recently, two patients with aquagenic pruritus have been reported with a good, but ephemeral response to NB-UVB (Xifra, Carrascosa et al. 2005).

In HIV patients with pruritus, UVB produced significant relief of pruritus in an open study with 21 patients (33% primary pruritus, 66% eosinophilic folliculitis) (Lim, Vallurupalli et al. 1997).

In a single case report a patient with Hodgkin's disease responded well to BB-UVB (Kaptanoglu and Oskay 2003).

Expert recommendation: UV therapy can be applied for CP. The mode of UV phototherapy depends on the underlying disease. UVA as well as UVB (NB-UVB / BB-UVB) as well as a combination of UVA/UVB relieve CP in certain diseases. UV phototherapy can be used in combination with topical and/or systemic treatment except for calcineurin inhibitors and immunosuppressant drugs.

4.6 Psychosomatic therapy (Relaxation techniques and psychotherapy)

The vicious itch-scratch cycle has to be taken into account when a patient is treated for CP. In addition to causal and symptomatic therapy, behavioural therapy to avoid scratching should be considered, e. g. conscious suppression of the reflex by intense concentration, distraction or alternative scratching techniques such as habit reversal (Rosenbaum and Ayllon 1981). This is very important in patients with prurigo nodularis who might show an unconscious automatic scratching behaviour.

Adjuvant psychosocial programmes are most effective in AD (Gieler, Kupfer et al. 2000; Staab, von Rueden et al. 2002; Stangier, Ehlers et al. 2004; Staab, Diepgen et al. 2006; Weisshaar, Diepgen et al. 2008). Such programmes include strategies for breaking the vicious circle of itching and scratching, relaxation and stress management techniques as well as strategies for dealing with relapses. A similar educational programme was developed for patients with CP (Bathe, Matterne et al. 2009; Evers, Duller et al. 2009). It is currently established for in-patient hospital treatment of patients with pruritic dermatoses using behavioural therapy in the context of an integrated psychosomatic treatment (Hoegl, Fichter et al. 1998; Lange, Zschocke et al. 1999). In patients with coexisting depression, psychotherapy in combination with psychotropic medication can be helpful even to treat pruritus of different etiology (Gupta 1995). Most publications on psychotherapeutic/ psychopharmacologic interventions, however, refer to small groups or single case reports. In neurotic excoriations, combined psychopharmacotherapy is also often indicated (Phillips and Robson 1988; Gupta 1995; Arnold, Auchenbach et al. 2001; Phillips 2002).

Expert recommendation: Relaxation techniques and education programmes for CP patients are useful as a complementary treatment for managing CP.

Table 1: Drugs that may induce or maintain chronic pruritus (without a rash)

Class of drug	Substance (examples)
ACE inhibitors	captopril, enalapril, lisinopril
Antiarrhythmic agents	amiodarone, disopyramide, flecainide
Antibiotics	amoxicillin, ampicillin, cefotaxime, ceftriaxone, chloramphenicol, ciprofloxacin, clarithromycin, clindamycin, cotrimoxazole, erythromycin, gentamycin, metronidazole, minocycline, ofloxacin, penicillin, tetracycline
Antidepressivants	amitryptylin, citalopram, clomipramin, desipramine, doxepin, fluoxetine, fluvoxamine, imipramine, lithium, maprotiline, mirtazapine, nortriptyline, paroxetine, sertraline
Antidiabetic drugs	glimepiride, metformin, tolbutamide
Antihypertensive drugs	clonidine, doxazosin, hydralazine, methyldopa, minoxidil, prazosin, reserpine
Anticonvulsants	carbamazepine, clonazepam, gabapentin, lamotrigine, phenobarbital, phenytoin, topiramate, valproic acid
Anti-inflammatory drugs	acetylsalicylic acid, celecoxib, diclofenac, ibuprofen, indometacin, ketoprofen, naproxen, piroxicam
AT II antagonists	Irbesartan, telmisartan, valsartan
Beta blockers	acebutolol, atenolol, bisoprolol, metoprolol, nadolol, pindolol, propranolol
Bronchodilators, mucolytic agents, respiratory stimulans	aminophylline, doxapram, ipratropium bromide, salmeterol, terbutaline
Calcium antagonists	amlodipine, diltiazem, felodipine, isradipine, nifedipine, nimodipine, nisoldipine, verapamil
Diuretics	amiloride, furosemide, hydrochlorothiazide, spironolactone, triamterene
Hormones	clomifene, danazol, oral contraceptives, estrogens, progesterone, steroids, testosterone and derivates, tamoxifen
Immunsuppressive drugs	cyclophosphamide, ciclosporin, methotrexate, mycophenolatmofetil, tacrolimus (bis 36%), thalidomide
Antilipids	clofibrate, fenofibrate, fluvastatin, lovastatin, pravastatin, simvastatin
Neuroleptics	e. g. chlorpromazine, haloperidol, risperidone
Plasma expanders, blood supplying drugs	Hydroxyethyl starch, pentoxifylline
Tranquilizers	alprazolam, chlordiazepoxidd, lorazepam, oxazepam, prazepam
Uricostatics	allopurinol, colchicine, probenecid, tiopronin

Table 2: Laboratory and technical investigations in chronic pruritus due to systemic diseases

Laboratory and technical screening-basic	Creatinine, AST, ALT, alkaline phosphatase, bilirubin, TSH, complete blood count, glucose, chest X-ray, (Ca, y-GT, stool test for parasites in genito-anal pruritus)
Metabolic and endocrine diseases	
Renal insufficiency	Lab I.: Creatinine (and urea for elderly) Lab II: phosphate, PTH, HCO3, urinalysis, urine protein concentration. Tech: sonography of the kidneys, CT or MRI
Liver diseases with or without cholestasis	Lab I: y-GT, AP, bilirubin, AST,ALT, (and HB-,HC-antibodies, if a risk-patient) Lab II: LDH, AMA, ANA, Anti-HBc-Ab, HBs-Ag, Anti-HCV-Ab, anti-smooth muscle Ab, antiactin Ab Tech: sonography of the liver, CT or MRT, (Magnetic resonance cholangiogram (MRC) or endoscopic retrograde cholangiogram (ERC) to rule out primary sclerosing cholangitis)
Hyperparathyroidism	Lab I: PTH, Calcium (only, if symptoms or signs of hyperparathyroidism ("stones, bones, moans and abdominal groans (and psychiatric overtones") Lab II: phosphate, Vit D (1,25-Vit D, 25 Vit-D) Tech: sonography of the parathyroid glands, scintigraphy, MRI
Hyper- and hypothyroidism	Lab I: TSH, Lab II: T3, T4, MAKs and TRAKs Tech: sonography of the thyroid glands, Iodine-scintigraphy
Anemia	Lab I: complete blood count including MCV and MCHC, LDH Lab II: ferritin, transferrin saturation (TSAT)– optionally: Lab III: Bone marrow aspiration with iron staining
Iron deficiency	Lab I: ferritin Lab II: transferrin saturation (TSAT**)**
Malabsorption	(Lab-tests only in case of a typical history (pancreas disease, intestinal resection) or symptoms like chronic diarrhea or steatorrhea and weight loss.) Lab I: Serum protein, serum albumine, calcium, blood count, gliadin-antibody Lab II: Vitamin A (hyperkeratosis by Vitamin A deficiency), Vitamin B12 (neuropathy by Vitamin B deficiency) Tech: endoscopy with biopsy

Other diseases	
Pruritus of the elderly	Lab I: Lab screening: creatinine, ALT, AST, alkaline phosphatase, bilirubin, TSH, full blood count, + BUN, (+ estimated creatinine clearance)
Infective diseases	**HIV** HIV-antibodies, Westernblot **Parasitoses including Helminthosis, Giardia lamblia (rare)** stool culture and microscopic examination
Haematological disorders	**Polycythemia vera** Lab I: blood count, thrombocytes, sedimentation rate, Lab II: :to rule out secondary erythrocytosis: O2 saturation, erythropoietin (EPO) level (renal cell carcinoma or polycystic kidneys) Lab III: bone marrow with chromosomal aberrations, Tech: sonography, CT or MRI of the spleen, **Lymphoma** Lab I: blood count, blood smear, thrombocytes, sedimentation rate, Lab II: Bone marrow with chromosomal aberrations, Tech: sonography, CT or MRI of the abdomen, thorax and additional affected areas, (PET)
Neurological diseases	**Multiple sclerosis** Lab : cerebrospinal fluid analysis (oligoclonal bands?) Tech: EEG, MRI, CT of the brain und functional tests **Brain tumors** Lab: cerebrospinal fluid analysis with histopathology Tech: EEG, MRI, CT of the brain **Notalgia paresthetica** MRI of the thoracic spine **Brachioradial pruritus** MRI of the thoracic and cervical spine
Psychiatric or psychosomatic diseases	(e.g., depression, affective disorders, hallucinosis, obsessive and compulsory disorders, schizophrenia, eating disorders) Psychiatric and psychosomatic exploration, psychiatric short questionnaire for depressive and anxiety disorder
Pregnancy with or without cholestasis	Lab I: y-GT, AP, bilirubin, AST, ALT, bile acids Lab II: Virus screen: hepatitis A,B,C, Epstein Barr and cytomegalovirus, a liver autoimmune screen for chronic active hepatitis and primary biliary cirrhosis (anti-smooth muscle and antimitochondrial antibodies) (Girling 2006) Tech: liver ultrasound
Drug induced pruritus	Lab I: y-GT, AP, bilirubin, AST; ALT, LDH Skin biopsy in case of HES exposition.

Table 3: Diagnostic algorithm

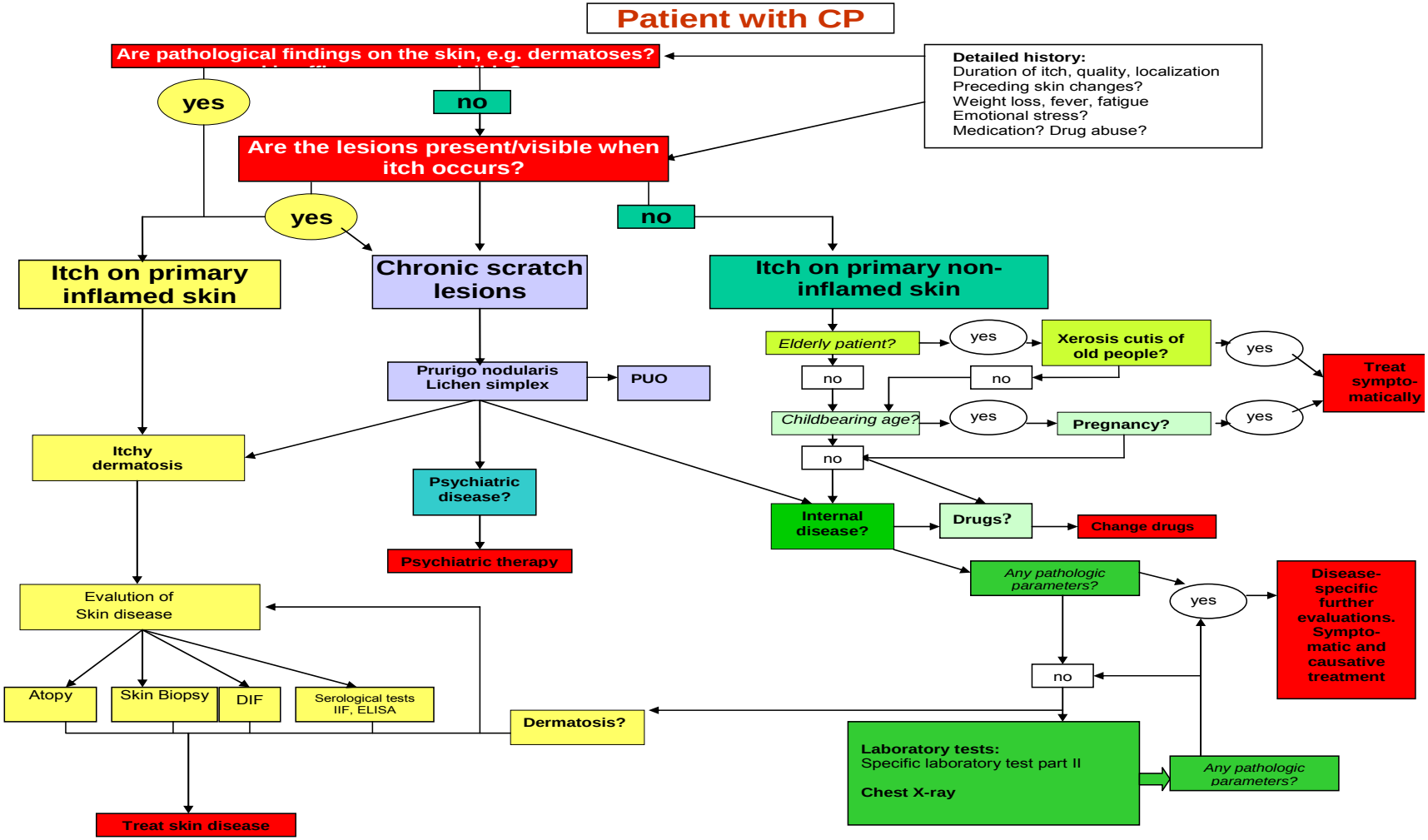

Table 4: General measures for treating chronic pruritus

Avoidance of	Factors that foster dryness of the skin, as e. g. dry climate, heat (e. g. sauna), alcoholic compresses, ice packs, frequent washing and bathing
	Contact with irritant substances (e.g. compresses with rivanol, chamomile, tea-tree oil)
	Very hot and spicy food, large amounts of hot drinks and alcohol
	Excitement, strain, negative stress
	In atopic patients: avoidance of aerogene allergens (e. g. house dust resp. house dust mites) which may aggravate pruritus
Application of	mild, non-alcaline soaps, moisturizing syndets and shower / bathing oils
	Luke-warm water, bathing time not exceeding 20 minutes. In patients with dermatoses: after contact with water, the skin should be dabbed dry without rubbing it because damaged and inflamed skin might worsen
	soft clothing permeable to air e.g. cotton, silver based textiles
	Skin moisturizer on a daily basis especially after showering and bathing
	Topicals with symptomatic relief especially for pruritus at night: creams/ lotions / sprays with e.g. urea, campher, menthol, polidocanol, tannin preparations wet, cooling or fat-moist-wrappings, wrappings with black tea, short and lukewarm showers
Relaxation techniques	Autogenic training, relaxation therapy, psychosocial education
Education	coping with the vicious circle of itch-scratch-itch educational training programs e.g. for children suffering from atopic dermatitis or chronic pruritus (Staab, Diepgen et al. 2006; Weisshaar, Diepgen et al. 2008; Bathe, Matterne et al. 2009)

Table 5: Therapeutic options in CKD-associated pruritus

Antipruritic effects confirmed in controlled studies	- Activated charcoal 6g/d (Bernhard 1994) - Gabapentin 300 mg 3 x /week postdialysis (Gunal, Ozalp et al. 2004) - Gamma-linolenic acid cream 3x/d (Chen, Chiu et al. 2006) - Capsaicin 3-5x/d (Breneman, Cardone et al. 1992; Tarng, Cho et al. 1996) - UVB phototherapy (Gilchrest, Rowe et al. 1979) - Acupuncture at the Quchi (LI11) acupoint (Che-Yi, Wen et al. 2005) - Nalfurafine intravenously postdialysis (Wikstrom, Gellert et al. 2005) - Thalidomide 100 mg/d (Silva, Viana et al. 1994)
Equivocal effects in controlled studies	- Naltrexone 50 mg/d (Peer, Kivity et al. 1996; Pauli-Magnus, Mikus et al. 2000) - Ondansetron 8 mg orally or i.v. (Ashmore, Jones et al. 2000; Murphy, Reaich et al. 2003)
Antipruritic effects confirmed in case reports	- Cholestyramine (Bernhard 1994) - Tacrolimus ointment 2x/d (Pauli-Magnus, Klumpp et al. 2000; Kuypers, Claes et al. 2004) - Cream containing structured physiological lipids with endocannabinoids (Szepietowski, Szepietowski et al. 2005) - Mirtazapine (Davis, Frandsen et al. 2003) - Cromolyn sodium (Rosner 2006) - Erythropoetin 36 IU/kg KG 3x/week (De Marchi, Cecchin et al. 1992) - Lidocaine 200 mg i.v./d (Bernhard 1994) - Ketotifen 1-2 mg/d (Francos, Kauh et al. 1991)

Table 6: Therapeutic options in hepatic and cholestatic pruritus

Antipruritic effects confirmed in controlled studies	• Cholestyramine 4-16 g/d (not in primarily biliary cirrhosis!) (Bergasa, Mehlman et al. 2000) • Ursodesoxycholic acid 13-15 mg/kg/d (Goulis, Leandro et al. 1999) • Sertraline 75-100mg/d (Mayo, Handem et al. 2007) • Rifampicin 300-600 mg/d (Ghent and Carruthers 1988) • Naltrexone 50 mg/d (Wolfhagen, Sternieri et al. 1997; Terg, Coronel et al. 2002) • Naloxone 0,2 µg/kg KG/min (Bergasa, Alling et al. 1995) • Nalmefene 20 mg 2x/d (Bergasa, Alling et al. 1999) • Propofol 10-15 mg i.v. (bolus), 1 mg/kg/h (i.v. infusion) (Borgeat, Wilder-Smith et al. 1992) • Thalidomide 100 mg/d (McCormick, Scott et al. 1994)
Equivocal effects in controlled studies	• Ondansetron 4 mg or 8 mg i.v. or 8 mg orally (Schworer and Ramadori 1993; Schworer and Ramadori 1993; O'Donohue, Haigh et al. 1997; Muller, Pongratz et al. 1998)
Antipruritic effects confirmed in case reports	• Phenobarbital 2-5 mg/kg KG/d (Raiford 1995) • Stanozolol 5 mg/d (Walt, Daneshmend et al. 1988) • Phototherapy: UVA, UVB (Fleischer 2000) • Bright light therapy (10.000 Lux) reflected toward the eyes up to 60 min twice/d (Bergasa, Link et al. 2001) • Etanercept 25mg sc. 2x/w (Epstein and Kaplan 2004) • Plasma perfusion (Fleischer 2000) • Extracorporeal albumin dialysis with Molecular Adsorbent Recirculating System (MARS) (Doria, Mandala et al. 2003; Mullhaupt, Kullak-Ublick et al. 2003; Bellmann, Feistritzer et al. 2004; Bellmann, Graziadei et al. 2004; Acevedo Ribo, Moreno Planas et al. 2005; Montero, Pozo et al. 2006) • Liver transplantation (Neuberger 2003)

Table 7: Antipruritic therapy of atopic dermatitis

Antipruritic therapy of atopic dermatitis[1]	
Antipruritic effects confirmed in controlled studies:	• Glucocorticosteroids (topical and oral) • Ciclosporin A • Leukotriene antagonists (e.g. zafirlukast) • Interferon gamma, i.c. • Tacrolimus ointment (2x/d) • Pimecrolimus cream (2x/d) • Doxepin 5% cream (2x/d) (Drake, Fallon et al. 1994; Drake and Millikan 1995)
Equivocal results:	• Antihistamines (topical and systemic) • Naltrexon 50 mg/ d (Brune, Metze et al. 2004) • Mycophenolatemofetil
Antipruritic effects confirmed in case reports:	• Antipruritic effects confirmed in case reports: • Macrolide antibiotics • Immunoglobuline, i.v. • UVA1-/UVB 311-Therapie • Capsaicin (3-5x/d)

[1] We refer to the current guideline for atopic dermatitis and Stander, S. and M. Steinhoff (2002). "Pathophysiology of pruritus in atopic dermatitis: an overview." Exp Dermatol **11**(1): 12-24. and table.

Table 8: Therapeutic options in polycythaemia vera

Effects confirmed in case reports	• Paroxetine 20mg/d (Diehn and Tefferi 2001; Tefferi and Fonseca 2002) • Hydroxyzine (Diehn and Tefferi 2001) • Fluoxetine 10mg/d (52 Tefferei 2002) • Aspirin (Fjellner and Hagermark 1979) • Cimetidine 900mg/d (Easton and Galbraith 1978; Weick, Donovan et al. 1982) • Pizotifen 0.5mg 3x/d (Fitzsimons, Dagg et al. 1981) • Cholestyramine (Chanarin and Szur 1975) • Ultraviolet B phototherapy (Baldo, Sammarco et al. 2002) • Photochemotherapy (PUVA) (Swerlick 1985; Jeanmougin, Rain et al. 1996) • Transcutaneous electrical nerve stimulation (Tinegate and McLelland 2002) • Interferon-alpha (de Wolf, Hendriks et al. 1991; Finelli, Gugliotta et al. 1993; Muller, de Wolf et al. 1995; Taylor, Dolan et al. 1996)

Table 9: Therapeutic options in aquagenic pruritus

Effects confirmed in case reports (Steinman and Greaves 1985; Wolf and Krakowski 1988; Shelley and Shelley 1998)	• Topical capsaicin 0,025%-1% thrice/d for 4 weeks • Glycerol trinitrate topically 2% • Transdermal application of scopulamin, topically 3% or 9% • Baths with sodium bicarbonate (0.5-1 kg/bath) • Bath and systemic PUVA, UVB (Menage, Norris et al. 1993; Jahn, von Kobyletzki et al. 1997; Martinez-Escribano, Quecedo et al. 1997; Xifra, Carrascosa et al. 2005) • Propranolol 10 to 80 mg/d • Clonidine 0.1 mg twice/d • Astemizol 10 mg/d • Ibuprofen (prior to bathing) • Pregabalin 150-300 mg/day • Antihistamines, e. g. hydroxyzine 25 mg/d, chlorpheneramin 8 mg/d, cetirizine, loratadine, fexofenadine, terfinadine • H2-blockers: cimetidine 900 mg/d • Opioid receptor antagonists, e. g. naltrexone 25-50 mg/d • Selective serotonin reuptake inhibitors, e. g. paroxetine 20 mg/d, fluoxetine 10 mg/d • Interferon-alpha 2b 5x 3 mil IE 1st week, 3x3 mil IE 2nd – 4th week
Effects confirmed in RCT:	• Acetylic salicylic acid 300-500 mg/day

Table 10: Stepwise symptomatic-therapeutic approach in chronic pruritus (> 6 weeks)

	Therapy
Step 1	• General therapeutic measures **(tab. 4)**, especially basic therapy with moisturizers • Initial symptomatic therapy: systemic H1 antihistaminics*, topical corticosteroids
Step 2	• Symptomatic causative adapted therapy **(tab. 5-9)** if origin is unknown
Step 3	• In pruritus of unknown origin or therapy refractory cases in the 2nd step: symptomatic topical and/or systemic therapy, e. g. capsaicin, calcineurin inhibitors, cannabinoid agonists, naltrexone, gabapentin, UV photo therapy, immunosuppressives (ciclosporin)
Concomitant treatment in every step	• Diagnostic and treatment of underlying disease • General therapeutic measures **(tab. 4)** • **In sleep disorders: sedative H1-antihistaminics, tranquilizers, tricyclical antidepressants or neuroleptics** • Psychosomatic care, behavioural therapy for scratch behaviour • In erosive scratch lesions: disinfecting measures, topical corticosteroids

* There is no evidence for the following diagnoses: cholestatic pruritus, nephrogenic pruritus

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