European Guideline on Chronic Pruritus
In cooperation with the European Dermatology Forum (EDF) and the European Academy of Dermatology and Venereology (EADV)

Developed by the Guideline Subcommittee “Pruritus” of the
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Abstract

Pruritus is a frequent symptom in medicine. Population-based studies show that every 5th person in the general population has suffered from chronic pruritus (CP) at least once in the lifetime with a 12-month incidence of 7%. In patient populations its frequency is much higher depending on the underlying cause, ranging from around 25% in haemodialysis patients to 100% in skin diseases such as urticaria and atopic dermatitis (AD). Pruritus may be the result of a dermatological or non-dermatological disease. Especially in non-diseased skin it may be caused by systemic, neurological or psychiatric diseases, as well as being a side effect of medications. In a number of cases CP may be of multifactorial origin. Pruritus needs a precise diagnostic work-up. Management of CP comprises treatment of the underlying disease and topical treatment modalities, including symptomatic antipruritic treatment, ultraviolet phototherapy and systemic treatment. Treating CP needs to be targeted, multimodal and performed in a step-wise procedure requiring an interdisciplinary approach. We present the updated European guideline on chronic pruritus by a team of European pruritus experts from different disciplines.

This version is an updated version of the guideline that was published in 2012 and updated in 2014 (www.euroderm.org).

Conflict of Interest: see table enclosed

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Abbreviations and explanations

AD	Atopic dermatitis
AEP	Atopic eruption of pregnancy
CGRP	Calcitonin gene-related peptide
CKD	Chronic kidney disease
CNS	Central nervous system
CNPG	Chronic nodular prurigo
CP	Chronic pruritus (longer than 6 weeks)
CPG	Chronic prurigo
CSU	Chronic spontaneous urticaria
DIF	Direct immunofluorescence
ICP	Intrahepatic cholestasis of pregnancy
IFSI	International Forum on the Study of Itch
IIF	Indirect immunofluorescence
IL	Interleukin
Itch	Synonym of pruritus
NRS	Numerical rating scale
NSAID	Non-steroidal anti-inflammatory drugs
PAR	Proteinase-activated receptor
PBC	Primary biliary cirrhosis
PEP	Polymorphic eruption of pregnancy
PG	Pemphigoid gestationis
Pruritus	A skin sensation that elicits the urge to scratch
PUO	Pruritus of undetermined origin
PTH	Parathyroid hormone
PV	Polycythaemia vera
RCT	Randomised controlled trials
SSRI	Selective serotonin re-uptake inhibitors
TRP	Transient receptor potential
UP	Uremic pruritus
UV	Ultraviolet
VAS	Visual analogue scale
VIP	Vasoactive intestinal peptide
VRS	Visual rating scale

1 The challenge of writing this guideline

Chronic pruritus (CP) is a frequent symptom in the general population and in many skin and systemic diseases (Weisshaar and Dalgard 2009). Due to its severity and the fact that it is frequently refractory to therapy, it causes a high burden and impairs quality of life. This guideline addresses all causes and types of CP including chronic prurigo. In its early stage, CP is considered a symptom of the underlying disease. However, with time, CP may develop its own dynamics that are no longer linked to the course of the underlying disease. In this stage, and much like chronic pain, this can be considered a distinct syndrome (CP syndrome) or even a disease in its own right. The observation that different patients with CP report similar severity, course and burden of CP despite the diversity of the underlying origins supports the view that CP requires independent consideration. Nevertheless, this guideline presents a diagnostic and therapeutic approach that is applicable to all types of CP. However, as a consequence of the diversity of possible underlying diseases, each form of CP should also be considered individually. Studies have demonstrated that early intervention in certain types of CP may lead to a significant improvement [e.g. therapy of polycythemia vera-associated aquagenic pruritus with janus kinase (JAK) inhibitors].

Still, there is a significant lack of randomised controlled trials (RCTs) investigating different types of CP in detail, which can be explained by the diversity and complexity of this symptom, the multifactorial aetiologies of pruritus and the lack of well-defined outcome measures, biomarkers and therapy targets. To complicate matters, RCTs exist for some types of pruritus, but with conflicting results. However, new therapies for improved medical care have been suggested and are summarised in this guideline. Expert recommendations are also provided. In addition, if the underlying cause is detected, disease-specific guidelines should be consulted [e.g. atopic dermatitis (AD) (Misery, Alexandre et al. 2007, Magerl, Borzova et al. 2009, Darsow, Wollenberg et al. 2010, Wollenberg, Oranje et al. 2016), urticaria (Zuberbier, Aberer et al. 2018), scabies (Salavastru, Chosidow et al. 2017), adult palliative care (Siemens, Xander et al. 2016)]. The health care systems in many countries and their social economic situation with ever diminishing financial resources increase the need for guidelines. These recommendations are based on a consensus of participating countries, while also

allowing for adaptation to country-specific treatment modalities and health care structures. Furthermore, it should be borne in mind that several 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. The guideline addresses all medical disciplines that work with patients suffering from CP.

This updated and revised guideline considers the Appraisal of Guideline Research and Evaluation Instrument (AGREE 2015) and the methods of the GRADE working group (www.gradeworkinggroup.org). All consented recommendations are written at the end of each section on treatment in Sect. 6.

2 Definitions and clinical classification

The definitions presented in this guideline are based on the terminology defined by the International Forum for the Study of Itch (IFSI). The European participants of this guideline agreed to use this terminology. All contributors accept pruritus and itch to be synonymous. This guideline also defines pruritus/itch as a sensation that provokes the desire to scratch. Patients do not only scratch; they also rub, pinch or damage their skin with devices (all summarised from this point onward under the term scratching). In some diseases involving itch, patients' scratching does not lead to skin damage (e.g. urticaria); in other diseases, scratching leads to a worsening of itch (e.g. urticaria factitia) and is accordingly avoided. These differences hinder scratching or scratch lesions from serving as common objective markers for the severity of itch.

According to the IFSI, CP is defined as pruritus lasting 6 weeks or longer (Ständer, Weisshaar et al. 2007). This is a practical distinction defined by clinicians in order to facilitate the decision to perform a diagnostic work-up. In some cases, pruritus may precede the diagnosis of the underlying disease by years (premonitory pruritus); in others, it is the early sign of a neoplastic disease such as Hodgkin lymphoma (paraneoplastic disease). In line with the 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 aetiology” should be avoided as in most clinically well-defined forms of pruritus the

neurobiological mechanisms of CP are unknown [e.g. chronic kidney disease (CKD)-associated pruritus].

The IFSI classification comprises a clinical distinction of patients with Group I pruritus on primarily diseased/inflamed skin, Group II pruritus on normal skin and Group III pruritus with chronic secondary scratch lesions (Ständer, Weisshaar et al. 2007). According to this classification, the aetiology of CP is classified into categories as “dermatological”, “systemic”, “neurological”, “somatoform”, “mixed origin” and “others” (Ständer, Weisshaar et al. 2007). Neurological pruritus refers mostly to diseases involving the central and/or peripheral nervous system resulting in diseased or malfunctioning neurons firing action potentials with origins at any point along the afferent pathway (Twycross, Greaves et al. 2003, Oaklander 2012). In most cases, this is better described as neuropathic pruritus inducing an overlap of pain, pruritus and par- or dysaesthetic sensations. Somatoform pruritus is defined as pruritus where psychic, psychiatric and psychosomatic factors play a critical role in the onset, intensity, aggravation or persistence of the pruritus.

3 Epidemiology of chronic pruritus

Data on the prevalence of CP is very limited. The prevalence of CP seems to increase with age (Rea, Newhouse et al. 1976), but epidemiological studies are lacking. It is estimated that about 60% of the elderly (over 65 years of age) suffer from mild to severe occasional pruritus every week (Zylicz, Twycross et al. 2004), referred to as pruritus in the elderly. A population-based cross-sectional study in 19,000 adults showed that about 8%–9% of the general population experienced acute pruritus, which was a dominant symptom across all age groups (Dalgard, Svensson et al. 2004). Moreover, it was revealed that pruritus is strongly associated with chronic pain (Dalgard, Dawn et al. 2007). Recent surveys indicate a point prevalence of CP to be around 13.5% in the general adult population (Matterne, Apfelbacher et al. 2011, Matterne, Apfelbacher et al. 2013) and 16.8% in employees seeking early detection cancer screenings (Ständer, Schäfer et al. 2010). The 12-month-prevalence of CP was 16.4% and its lifetime prevalence 22.0% in a German population-based cross-sectional study (Matterne, Apfelbacher et al. 2011). All these data suggest a higher prevalence of CP in the general population than previously reported (Matterne, Apfelbacher et al. 2011). For the first time, a recent study found a 12-month cumulative incidence of CP of

7% and incident pruritus was significantly associated with higher age (Matterne, Apfelbacher et al. 2013). Multivariate analysis revealed eczema, dry skin, asthma, liver disease, an elevated body mass index and higher anxiety scores to be determinants of prevalent CP (Matterne, Apfelbacher et al. 2013).

CP may be due to both dermatological and systemic diseases. However, the origin of pruritus is unknown in up to 20% of affected patients (Weisshaar and Dalgard 2009). For example, pruritus is present in all patients with AD and urticaria (Yosipovitch, Goon et al. 2002) and in about 80% of psoriatic patients (Szepietowski, Reich et al. 2002, Szepietowski, Reich et al. 2004). Systemic diseases such as primary biliary cirrhosis (PBC) and CKD are associated with CP in 80%–100% and 25%–70%, respectively (Szepietowski and Salomon 2004); however, the great variability of numbers may be explained by a lack of disease definition and prevalence estimates. The first representative cohort study investigating CP in haemodialysis patients showed 25.2% to suffer from CP (point prevalence), while the lifetime prevalence was 35.2% (Weiss, Mettang et al. 2016). Pruritus is a frequent symptom in patients with Hodgkin's lymphoma, occurring in more than 30% of this patient group (Weisshaar and Dalgard 2009). In a retrospective study on 139 patients with CP, most cases of severe and long-lasting itch were found in patients with multiple systemic diseases and in patients with pruritus of unknown origin, while pruritus of the scalp and face was often a presenting symptom of psychiatric disease (Ferm, Sterner et al. 2010).

Only few studies have addressed the frequency of pruritus in primary care. According to the Australian BEACH Program, a continuous national study of general practice activity, pruritus was the presenting complaint for 0.6% of consultations, excluding perianal, periorbital or auricular pruritus (Britt, Pan et al. 2004). In the UK, the fourth national study of morbidity statistics from general practice (McCormick, Fleming et al. 1995) was conducted in 1991/1992 with 502,493 patients (1% sample of England and Wales), resulting in 468,042 person-years at risk. Pruritus and related conditions were present in 1.04% of consultations (male, 0.73%; female, 1.33%). In Crete, where patients with cutaneous disorders mostly present to hospitals rather than to primary care centres, PUO was diagnosed in 6.3% of 3,715 patients in 2003 (Symvoulakis, Krasagakis et al. 2006). In Germany and the Netherlands the prevalence of pruritus as a reason for consultation in primary care resulted in approximately

0.7% of all consultations, most of these resulting in a diagnosis of skin disease (SESAM2 study from 1999–2000, unpublished data from the Dutch Transition project from 1995 to 2003) (Frese, Herrmann et al. 2011).
The reader is referred to Sect. 4.2 for a more detailed discussion of the epidemiology of CP in specific patient populations..

4 The clinical picture of chronic pruritus

4.1.1 Chronic Pruritus in lesional and non-lesional skin

CP may occur as a common symptom in patients with dermatoses with primary skin lesions and systemic, neurologic and psychiatric/psychosomatic diseases without primary skin lesions (Ständer et al. 2007). In the three latter instances, the skin may appear normal or have skin lesions induced by scratching. In chronic and severe cases, patients can develop chronic prurigo (CPG), which may present as chronic nodular prurigo (CNPG) or other subtypes (Pereira, Steinke et al. 2018). In these cases, a clinical diagnosis is difficult to establish and diagnostics should be performed. Systemic diseases frequently accompanied by pruritus are summarised in Table 1. In recent years, several entities of pruritus on inflamed and normal skin have been characterised in more detail. Some frequent patient populations and systemic diseases inducing CP are presented in the following sections.

4.1.2 Pruritus in kidney disease

The pathophysiology of CKD-associated pruritus is unknown. Implicated mechanisms have included direct metabolic factors: increased concentrations of divalent ions (calcium, magnesium), parathyroid hormone (PTH), histamine and tryptase, dysfunction of peripheral or central nerves, the involvement of opioid receptors (μ- and κ-receptors) and xerosis cutis (dry skin) have been suggested as likely candidates (Blachley, Blankenship et al. 1985, Stockenhuber, Sunder-Plassmann et al. 1987, Stahle-Backdahl, Hagermark et al. 1989, Peer, Kivity et al. 1996, Pauli-Magnus, Mikus et al. 2000, Dugas-Breit, Schopf et al. 2005, Wikstrom, Gellert et al. 2005, Duque, Thevarajah et al. 2006, Kimmel, Alscher et al. 2006). Some data point to a possible role for micro-inflammation, which is relatively frequent in uraemia (Mettang, Pauli-Magnus et al. 2002, Kimmel, Alscher et al. 2006). Two uremic toxins, p-cresylsulfate and indoxylsulfate, were recently

suggested to be involved in the pathogenesis of CP in kidney disease (Wang, Lu et al. 2016).

One representative study on CP in 177 haemodialysis patients showed that 43.5% had normal looking skin (IFSI II), 37.9% had secondary scratch lesions including CPG (IFSI III) and 18.6% had a skin disease (IFSI I) (Hayani, Weiss et al. 2016).

4.1.3 Pruritus in hepatobiliary diseases (cholestatic pruritus)

CP is a frequent symptom in patients with hepatobiliary disease and cholestasis due to mechanical obstruction, metabolic disorders or inflammatory diseases (Bergasa 2005, Beuers, Kremer et al. 2014, Kremer, Bolier et al. 2014). It is termed cholestatic pruritus (ChP), although cholestasis is not a prerequisite of pruritus related to diseases of the liver. ChP may be quite severe and can even precede the diagnosis of, e.g. primary biliary cholangitis (PBC) by years (Bergasa, Mehlman et al. 2000, Kremer, Namer et al. 2015). Pruritus is less frequent in patients with infectious liver disease (hepatitis B or C) or toxic liver disease (e.g. alcohol-induced). The true prevalence of CP in hepatobiliary diseases is not known due to lacking epidemiological data. It seems that CP is most frequent in PBC, primary sclerosing cholangitis (PSC) and secondary sclerosing cholangitis (SSC). CP usually peaks in the evening and night, frequently presenting without any primary skin lesion but sometimes with secondary scratch lesions and CPG. It is often generalised, affecting palms and soles in the early stage (Cacoub, Poynard et al. 1999).

It has recently been shown that increased serum autotaxin (ATX) [the enzyme that metabolises lysophosphatidylcholine (LPC) into lysophosphatidic acid (LPA)] levels, and thereby increased LPA levels, are specific for pruritus in cholestasis, including intrahepatic cholestasis of pregnancy and paediatric cholestatic disorders (Beuers, Kremer et al. 2014, Kremer, Bolier et al. 2014, Kremer, Namer et al. 2015), but not for other forms of systemic pruritus (Kremer, Dijk et al.). Rifampicin significantly reduced itch intensity and ATX activity in pruritic patients. The beneficial antipruritic action of rifampicin may be explained partly by pregnane X receptor (PXR)-dependent transcription inhibition of ATX expression (Kremer, Dijk et al.). Successful treatment with μ-receptor opioid antagonists such as nalmefene and naltrexone supports the hypothesis that opioid receptors and a high opioid tone influences ChP (Bergasa, Schmitt et al. 1998).

4.1.4 Pruritus in metabolic and endocrine diseases

In endocrine disorders such as hyperthyroidism and diabetes mellitus, less than 10% of patients report pruritus (Neilly, Martin et al. 1986, Jabbour 2003). In patients with hypothyroidism, pruritus is most probably driven by xerosis of the skin. Patients with primary hyperparathyroidism do complain of itch in a substantial number of cases (Caravati, Richardson et al. 1969). The pathophysiology of pruritus in primary hyperparathyroidism is not known. These patients often experience a lack of vitamin D and minerals (e.g. zinc etc.), which probably contributes to CP. Iron deficiency may be associated with CP (Adams 1989). The mechanism for this is unknown. Iron overload as in haemochromatosis may lead to CP (Nestler 1983, Hamilton and Gould 1985). CP in metabolic and endocrine disease frequently occurs as generalised pruritus, but localised forms such as genital CP may occur, e.g. in diabetes mellitus (Neilly, Martin et al. 1986, Wahid and Kanjee 1998). The clinical picture is not specific, frequently accompanied by dry skin and sometimes showing secondary scratch lesions (IFSI III) (Weisshaar and Dalgard 2009).

4.1.5 Pruritus in malignancy

Several malignant disorders including tumours, bone marrow diseases, myeloproliferative and lymphoproliferative disorders may be accompanied by pruritus. The term “paraneoplastic pruritus” is used to describe pruritus in patients with cancer (Weisshaar, Weiss et al. 2015). The true frequency of this symptom in malignant disease is unclear and epidemiological data in this field are limited. One study in a cohort of cancer patients showed that 5.9% suffer from generalised itch (Kilic, Gul et al. 2007). Gastrointestinal tumours and haematological malignancies were among the tumours that most commonly cause pruritus (Kilic, Gul et al. 2007). Most of the patients affected do not exhibit specific dermatoses, but unaffected skin or non-specific eruptions with and without papules and excoriations. In general, the prevalence of pruritus in haematological malignancies is higher compared to non-haematological malignancies; it is estimated to be around 30% in Hodgkin lymphoma, around 15%–50% in non-Hodgkin lymphoma and around 15%–50% in polycythemia vera (PV) (Weisshaar, Weiss et al. 2015, Tefferi, Vannucchi et al. 2018). The mechanisms of pruritus in malignancy are still not understood. Several mediators and mechanisms have been discussed in the literature such as toxic products generated by the tumour itself, allergic reactions

to compounds released and a direct affect on the brain or nerves (in brain tumours), the latter being referred to as neuropathic pruritus (Bernhard 1994, Zylicz, Twycross et al. 2004). Recently, interleukin-31 (IL-31), a Th-2 cytokine, was found to be highly associated with itch in lymphoma and highly expressed in malignant T-cells (Singer, Shin et al. 2013). In PV, more than 50% of patients suffer from pruritus (Egli, Wieczorek et al. 1988, Diehn and Tefferi 2001, Tefferi, Vannucchi et al. 2018). Aquagenic pruritus with pinching sensations after contact with water is a characteristic but not necessary feature. It has been suggested that high levels of histamine released by the augmented numbers of basophilic granulocytes might trigger the itch (Gilbert, Warner et al. 1966). For PV this seems to be most pronounced in patients showing the JAK2 617V mutation (Siegel, Tauschert et al. 2013, Tefferi, Vannucchi et al. 2018).

Pruritus in Hodgkin's disease often starts on the legs and is most severe at night, but generalised pruritus soon ensues. Several factors such as secretion of leukopeptidases and bradykinin, histamine release and high IgE levels with cutaneous depositions may contribute to pruritus in lymphoma (Krajnik and Zylicz 2001). Patients with carcinoid syndrome may experience pruritus in addition to flushing, diarrhoea and cardiac symptoms (Brunner 1995).

A recent population-based cohort study in 8,744 patients with CP showed that CP without concomitant skin changes is a risk factor for undiagnosed haematological and bile-duct malignancy (Fett, Haynes et al. 2014). A nationwide Danish cohort study based on registry data showed a 1-year absolute cancer risk of 1.63%, and a 13% higher than expected number of both haematological and various solid cancers among patients with pruritus was found. This related in particular to haematological cancers, above all Hodgkin lymphoma (Johannesdottir, Farkas et al. 2014); however, the study was unable to differentiate between acute and chronic itch.

4.1.6 Pruritus in infectious diseases

Acute or chronic pruritus may occur with skin infections and infestations, among which scabies is the most prominent example (Serling, Leslie et al. 2011). Viral infections such as herpes simplex, herpes zoster and varicella can present with acute pruritus. CP may occur in 4% of herpes zoster patients, which is termed post-herpetic itch (Weisshaar and Dalgard 2009).

Some generalised infections are accompanied by pruritus. Above all, patients infected with human immunodeficiency virus (HIV) may develop CP, which can be the initial presentation of HIV infection. The true prevalence is not known but could be as high as 45% according to cross-sectional study (Kaushik, Cerci et al. 2014). In a significant number of HIV patients itching has no detectable cutaneous or systemic cause; however, HIV patients are prone to develop pruritic papular eruption (PPE), a major cause of CP in African HIV patients (Weisshaar, Apfelbacher et al. 2006, Weisshaar and Dalgard 2009). There is evidence for a high association between prurigo and HIV infection, but regional variations need to be considered (Weisshaar, Apfelbacher et al. 2006).

Whether toxocariasis infections lead to pruritus in a substantial number of patients remains to be confirmed (Afifi, Aubin et al. 2004). Pruritus has been reported in up to 15% of patients with chronic hepatitis C virus (HCV) infection and may be a presenting symptom (Maticic, Poljak et al. 2008).

4.1.7 Pruritus in neurological diseases

Space occupying lesions (tumours, abscesses, haemorrhage) of the nervous system and degenerative neurological diseases, e.g. multiple sclerosis, are rare causes of neuropathic pruritus with variable clinical presentation (Adreev and Petkov 1975, Canavero, Bonicalzi et al. 1997, Matsuura, Kimura et al. 2015, Misery 2016). Pruritus due to these neurological disorders may be the presenting symptom prior to diagnosis and could be transient, continuous or paroxysmal in nature (Wolking, Lerche et al. 2013). Entrapment syndromes of specific peripheral nerves such as notalgia paraesthetica, brachioradial pruritus, cheiralgia paraesthetica and meralgia paraesthetica present with pruritus localised to a specific anatomical area (Wallengren 1998, Savk and Savk 2005, Veien and Laurberg 2011, Mirzoyev and Davis 2013, Savk 2016). A typical accompanying clinical finding is the presence of various paraesthetic sensations, including a feeling of electrical current, prickling, tingling, burning and numbness. A recently recognised clinical phenomenon is generalised pruritus triggered by a localised neurological disorder, e.g. brachioradial pruritus (Kwatra, Stander et al. 2013, Zeidler and Ständer 2014). In a broader perspective, neuropathy of small cutaneous nerve fibres in dermatological disorders such as keloids, burns and post-zoster pruritus may also be classified under pruritus in neurological diseases (Lee, Yosipovitch et al. 2004, Goutos 2013, Dhand and Aminoff 2014, Mittal,

Srivastava et al. 2016). Analogously, pruritus in several systemic diseases associated with small fibre neuropathy is similarly included, the list being led by diabetes (Brenaut, Marcorelles et al. 2015).

4.1.8 Pruritus in psychiatric diseases

It is estimated that at least 32% of psychiatric patients on a psychiatric ward report itch (Mazeh, Melamed et al. 2008). A large population survey showed that adults with depression are twice as likely to experience itch (Dalgard, Lien et al. 2007) and that the severity of itch increases with symptoms of depression among adolescents (Halvorsen, Dalgard et al. 2009). The pathophysiological background seems to correlate with production and interaction of neuropeptides such as serotonin (Zhao, Huo et al. 2013). Individuals with anxiety tend to itch over time and this has implications for the therapeutic approach (Evers, Schut et al. 2016). Symptoms of obsessive compulsive disorder can manifest with CP, as seen in patients with skin picking (Craig-Muller and Reichenberg 2015, Tomas-Aragones, Consoli et al. 2016). "Scalp itch" is often a symptom of depression or a precursor to psychosis. CP can be a symptom in psychotic patients, manifesting as delusional parasitosis, a rare condition that is challenging to treat both for dermatologists and for psychiatrists (Lepping, Huber et al. 2015). Overall, the psychiatric population is little studied with regard to skin symptoms, but it is now established that psychiatric morbidity contributes to the pathophysiology of CP in the absence of skin disease (Pereira, Kremer et al. 2016).

4.1.9 Drug-induced chronic pruritus

Drug-induced pruritus without visible skin lesions accounts for approximately 5% of adverse cutaneous reactions. Almost any drug may induce pruritus by various pathomechanisms (Table 2) (Reich, Stander et al. 2009). Some may cause urticarial or morbilliform rashes presenting with acute pruritus. Furthermore, drug-induced hepatoxicity or cholestasis, as well as drugs that cause xerosis, photoallergy or phototoxicity may produce CP on normal skin (Kaplan 1984). Increased release of pruritogens (histamine, serotonin, neuropeptides), neurological alterations and neuronal deposition in the skin have also been suggested, but the pathogenesis of drug-induced itch is not fully understood (Ebata 2016). Hydroxyethyl starch (HES), a compound used for fluid restoration, can induce generalised or localised CP in 12%–42% of treated patients (Metze,

Reimann et al. 1997). Duration depends on the cumulative dose, usually persisting for an average of 15 months (after HES deposits in the tissues have been metabolised). In approximately two-thirds of HES-induced pruritus it is generalised and presents without any skin lesions (Reich, Stander et al. 2009, Weisshaar and Dalgard 2009).

4.2 Specific patient populations

4.2.1 Chronic pruritus in the elderly

Only a small number of studies have investigated pruritus in the elderly. They are characterised by selection bias and differing endpoints (pruritic skin disease or itch). An American study of cutaneous complaints in the elderly identified pruritus as the most frequent, accounting for 29% of all complaints (Beauregard and Gilchrest 1987). A Turkish study in 4,099 elderly patients found that pruritus was the most common skin symptom, affecting 11.5% of patients. Women were more frequently affected (12.0%) than men (11.2%). Patients older than 85 years showed the highest prevalence (19.5%) and pruritus was present more frequently in winter months (12.8%) (Yalcin, Tamer et al. 2006). In a Thai study, pruritic diseases were the most common skin complaint (41%) among the elderly, while xerosis was identified as the most frequent ailment (38.9%) in a total of 149 elderly patients (Thaipisuttikul 1998).The exact mechanisms of CP in the elderly are unknown. Pathophysiological changes of the aged skin, decreased function of the stratum corneum, xerosis cutis, co-morbidities and polypharmacy may all contribute to its aetiology (Sommer, Hensen et al. 2007).

4.2.2 Chronic pruritus in pregnancy

There are no epidemiological studies assessing the prevalence of CP in pregnancy. Pruritus is the leading dermatological symptom in pregnancy, estimated to occur in about 18% of pregnancies (Weisshaar, Diepgen et al. 2005). It can present as specific dermatoses of pregnancy [polymorphic eruption of pregnancy (PEP), pemphigoid gestationis (PG), intrahepatic cholestasis of pregnancy (ICP), atopic eruption of pregnancy (AEP)], but may also occur in other dermatoses coinciding by chance with pregnancy or in pre-existing dermatoses (Holmes 1988, Weisshaar, Diepgen et al. 2005, Ambros-Rudolph, Mullegger et al. 2006, Girling 2006). Indeed, one of every five consultations for pruritus in

pregnancy is not related to the specific dermatosis of pregnancy (Roger, Vaillant et al. 1994).

PEP is one of the most common gestational dermatoses, affecting around one in 160 pregnancies. While PG, PEP and ICP characteristically present in late pregnancy, AEP starts before the third trimester in 75% of cases (Ambros-Rudolph, Mullegger et al. 2006, Weisshaar and Dalgard 2009). ICP is characterised by severe pruritus without any primary skin lesions; however, secondary skin lesions occur due to scratching. It is more prevalent among native Indians in Chile (27.6%) and Bolivia (13.8%) depending on ethnic predisposition and dietary factors (Reyes, Gonzalez et al. 1978, Reyes, Taboada et al. 1979). ICP has decreased in both countries, e.g. to 14% in Chile. ICP is more common in women of advanced maternal age, multiple gestations, a personal history of cholestasis on oral contraceptives and during winter months. Scandinavian and Baltic countries are also more affected (1%–2%). In Western Europe and North America ICP is observed in 0.4%–1% of pregnancies (Reyes, Gonzalez et al. 1978, Reyes, Taboada et al. 1979, Clark, Dwarakanath et al. 1999). PEP is one the most common gestational dermatoses, affecting about one in 160 pregnancies. While PG, PEP and ICP characteristically present in late pregnancy, AEP starts before the third trimester in 75% of cases (Ambros-Rudolph, Mullegger et al. 2006, Weisshaar and Dalgard 2009). ICP is characterised by severe pruritus without any primary skin lesions, but secondary skin lesions occur due to scratching. It is a hormonally triggered, reversible cholestasis occurring in late pregnancy (late second or third trimester) in genetically predisposed women. The prevalence is around 1%, but varies: it is higher in Scandinavia, South America and South Africa (Saverall, Sand et al. 2015). The aetiopathogenesis is multifactorial and involves genetic, hormonal and environmental factors such as seasonal variability and dietary factors (Ozkan, Ceylan et al. 2015).

4.2.3 Chronic pruritus in children

There are no epidemiological studies assessing the prevalence of CP in children (Weisshaar, Diepgen et al. 2005, Weisshaar and Dalgard 2009). The spectrum of differential diagnosis of CP in children is wide (Weisshaar, Diepgen et al. 2005, Metz, Wahn et al. 2013), but is dominated by skin diseases, in particular AD. The cumulative prevalence of AD is between 5% and 22% in developed countries. The German Atopic Dermatitis Intervention Study (GADIS) showed a significant

correlation between the intensity and severity of pruritus in AD and sleeplessness (Staab, Diepgen et al. 2006, Weisshaar, Diepgen et al. 2008). Chronic spontaneous urticaria (CSU) is a source of pruritus in approximately 3% of children (Gaig, Olona et al. 2004), for which a complete characterization of the disease is needed.

A Norwegian cross-sectional questionnaire-based population study in adolescents revealed a pruritus prevalence of 8.8%. Pruritus was associated with mental distress, gender, sociodemographic factors, asthma, rhinoconjunctivitis and eczema (Halvorsen, Dalgard et al. 2009). Itching of mild to moderate severity may occur in acne (Lim, Chan et al. 2008, Reich, Trybucka et al. 2008).

If children are aged > 6 years, the visual analogue scale (VAS), numerical rating scale (NRS) or verbal rating scale can be employed (Wahlgren 2005). In order to accurately assess the impact of CP in a child's life, some recommended scales include Skindex-16, Skindex-Teen, infant's dermatology life quality index (Lewis-Jones 2001), children's dermatology life quality index (Lewis-Jones and Finlay 1995) and ItchyQoL (Desai, Poindexter et al. 2008). Instruments that measure the effect of the families' quality of life include the dermatitis family impact questionnaire (Lawson, Lewis-Jones et al. 1998). The course of advanced learning for the management of itch (CALM-IT) task force recommend a multidisciplinary and multidimensional approach for children CP (Metz, Wahn et al. 2013).

It must be assumed that systemic causes of CP in children are mostly based on genetic diseases or systemic diseases, e.g. biliary atresia or hypoplasia, familial hyperbilirubinemia syndromes, polycystic kidney disease or CKD (Weisshaar and Dalgard 2009, Wojtowicz-Prus, Kilis-Pstrusinska et al. 2016). Drug-induced pruritus without any specific skin symptoms appears to be rare in children (Weisshaar and Dalgard 2009). Common medications associated with CP in adults play a minor role in children due to limited use at that age.

5 Diagnostic management

5.1 Patient history and clinical examination

Patient history and clinical examination are key to clarifying the aetiology of pruritus, which in turn allows adequate treatment. A number of typical features in the patient history may be helpful and sometimes even diagnostic to identifying the

cause of pruritus, e.g. duration, localisation, time course of pruritus and trigger factors, as well as a detailed personal and family history. To obtain this information from the patient, it is helpful to go through their history with a patient history-based algorithm (Fig. 1). The following questions can help to compile a patient history:

1. Duration and onset of itch ("When did itch start?") enables a differentiation between acute and CP (more or less than 6 weeks) (Ständer, Weisshaar et al. 2007).
2. Localisation of pruritus ("Where does it itch?") makes it possible to distinguish localised pruritus from generalized pruritus.

   Localized pruritus is usually caused by itchy dermatosis, when it occurs at localisations where inflamed skin is already present. Localised itch on primarily non-inflamed skin is suggestive for neurological disease, especially when itch appears in an asymmetrical pattern (Oaklander 2011, Oaklander 2012, Stumpf and Ständer 2013, Cohen, Andrews et al. 2014, Brenaut, Marcorelles et al. 2015): unilateral localized pruritus on the back is typical for notalgia paraesthetica, whereas itch on lateral aspects of the arms (especially the forearms) is characteristic for brachioradial pruritus. Both diseases have a neuropathic origin (Savk, Savk et al. 2000, Cohen, Masalha et al. 2003, Savk and Savk 2005). Pruritus may occur in internal diseases, where it can occur in typical localisations, e.g. on the back and legs in CKD-associated pruritus (Ponticelli and Bencini 1995, Hayani, Weiss et al. 2016) and on the palms and soles in cholestatic pruritus. Localised vulvar pruritus can be a symptom of iron deficiency (Stäubli 1981).

   Generalised pruritus can be caused by itchy dermatosis even if the inflamed skin does not show generalised spread, e.g. in patients with psoriasis (Yosipovitch, Goon et al. 2000). However, generalised pruritus on primarily normal skin is highly suggestive for not only internal but also neuropathic or psychiatric diseases (Polat, Oztas et al. 2008) or use of a drug that causes CP. Interestingly, in one study, whole-body pruritus was found more frequently in patients with dermatosis than in pruritus due to systemic disease (Weisshaar, Apfelbacher et al. 2006).
3. Intermittent pruritus can be distinguished from constant itch by asking "When does it itch?". Intermittent pruritus can be a symptom of spontaneous urticaria. In patients with factitial urticaria, pruritus occurs intermittently, typically starting

as localised itch and generalising with scratching. Constant pruritus is typical for internal diseases, e.g. renal or liver diseases or pruritus in patients with malignant lymphoma.

4. The time course of pruritus ("When is itch at its maximum/minimum?") can be indicative for a number of diseases: nocturnal generalised pruritus in association with chills, fatigue and B symptoms (weight loss, fever and nocturnal sweating) is suggestive of malignancy such as Hodgkin's disease. Seasonal pruritus during wintertime ("winter pruritus") is found in exsiccation eczema in the elderly.
5. Identification of pre-existing skin diseases in the patient history is crucial, especially if pruritus on primarily inflamed skin is assumed. In such cases, a history of AD, psoriasis or lichen planus is suggestive that pruritus has occurred due to an exacerbation of the known disease. An atopic background should always be verified or excluded. It is not uncommon for an atopic disposition to be the only explanation for the onset of pruritus in patients with PUO. However, the most important question to classify pruritus regards skin condition at the time of initial onset of pruritus ("How did the skin look when itch first appeared?"): if pruritus first appeared on primarily diseased (inflamed) skin, pruritic dermatosis—which needs to be diagnosed—is causative. If pruritus appeared on normal looking skin ["pruritus on primarily non-diseased (non-inflamed) skin"], one should consider a systemic, neuropathic or psychiatric disease, drug side effects, pregnancy or dermatosis without visible skin changes (Ständer, Weisshaar et al. 2007).
6. History of pruritus ("How did pruritus or the skin develop over time?") shows the dynamic of the disease course. Trigger factors and the relationship between pruritus and specific activities can be important: pruritus appearing during physical activity can be caused by AD, cholinergic pruritus and cholinergic urticaria. Pruritus provoked by skin cooling after emerging from a warm shower/bath can be a sign of aquagenic pruritus, polycythaemia vera or xerosis cutis.
7. Intensity and quality of itch (burning, painful, stinging, prickling) are best quantified with special tools that have been developed for the assessment of pruritus. For intensity, validated categorical or continuous monodimensional scales, such as the NRS or VAS, are most commonly used. The quality of

pruritus is assessed in a descriptive way by use of itch questionnaires. A validated questionnaire for quality of life assessment is the ItchyQol (Krause, Kessler et al. 2013).

8. Knowledge of pre-existing internal diseases is of importance when pruritus on primarily non-inflamed skin is assumed. In a patient with chronic renal failure or cholestatic liver disease, the primary disease will initially be suspected to cause itch. Unfortunately, there are no defined laboratory cut-off values (e.g. blood creatinine levels) that are indicative for the causative role of an internal disease.
9. A complete history includes documentation of medication use and change of medication in the preceding 12 months prior to the onset of pruritus. Drugs that typically provoke pruritus include opioids, retinoids, antibiotics and new drugs for cancer therapy, especially epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR) inhibitors, as well as tyrosine kinase inhibitors. In patients with a history of previous surgery and infusion treatments, hydroxyethyl starch (HES) should be considered as a possible cause.
10. Family history is indicative of familial skin diseases or internal disorders that are accompanied by itch. Finally, the personal environment may be instructive: if multiple family members are affected by new-onset of pruritus, scabies or other parasites should be considered.

Clinical examination of the patient should always include a thorough inspection of the entire skin including scalp, nails, oral cavity and anogenital region. While examining skin lesions, the distinction between primary and secondary skin lesions is of the utmost importance, since this allows a distinction between the three clinical presentations of pruritus as proposed by the IFSI classification (Ständer, Weisshaar et al. 2007).

If primary skin lesions such as macules/erythema, vesicles, papulo-vesicles, blisters, pustules or wheals are observable and, according to the patient history, have been present since the onset of itch, pruritus on primarily diseased (inflamed) skin can be diagnosed. Further investigations can be performed to determine the underlying dermatosis, including skin biopsy, microbiological investigations and, in certain cases, laboratory testing (e.g. IgE, indirect immunofluorescence).

Secondary skin lesions encompass excoriations, ulcerations, necrosis, crusts, papules, nodules, lichenification, atrophy and scars, as well as hyper- and hypo-pigmentation of the skin. In patients with CP these lesions are most likely caused by scratching. If a patient with CP reports that no skin lesions were visible at onset, pruritus on primarily non-diseased (non-inflamed) skin can be diagnosed. An internal disease, medications, pregnancy or specific skin diseases could be causative. Laboratory and radiological investigations, adapted to the patient history and pre-existing diseases, are mandatory to obtain a final diagnosis.

If a patient presents with extensive scratch lesions with a duration of many months or years (e.g. CPG, CPGN), pruritus with chronic secondary scratch lesions is diagnosed. The underlying cause may be a systemic, neurological, psychiatric or dermatological disease. Skin biopsy, laboratory and radiological investigations, as well as procedures suited to the patient's history and pre-existing diseases will yield a final diagnosis.

In addition to examining the entire integument, a general physical examination should be performed in all patients with unclear pruritus, including palpation of abdominal organs and lymph nodes, and a rectal examination.

Expert recommendation: We recommend taking a detailed history of any patient with chronic pruritus. This should include general characteristics of pruritus (e.g. duration, time course, localisation, intensity and quality), knowledge of the personal history, including precise information on medication and family history. We recommend a complete dermatological examination.

5.2 Diagnostic algorithm and diagnostics

Laboratory screening, clinical and technical approaches and investigations are summarised in Tables 3 and 4. All this helps to follow a diagnostic algorithm (Fig. 1).

6 Therapy

6.1 Therapy: general principles including emollients

It is important to establish an individual antipruritic therapy regimen that takes into account the age of the patient, pre-existing diseases, medications as well as the quality and intensity of CP. Elderly patients, pregnant women and children need special attention (see Sects. 6.6.1, 6.6.2 and 6.6.3). As the care of patients with

CP often extends over a long period, with initial uncertainty about the origin of the pruritus, frustration regarding the failure of past therapies and general psychological stress frequently occurs. Taking a careful history on the occurrence and characteristics of pruritus is very important (see Sect. 5.1). The diagnostic procedures and therapy should be discussed with the patient in order to achieve the best possible concordance and compliance.

As a first step, the patient should be informed about general pruritus-relieving measures (Table 5). These include simple and helpful tips such as keeping room temperatures low and applying moisturisers to improve skin barrier and reduce itching. Although many patients report that cold showers reduce itch, no scientific studies have been performed to confirm this observation. On the other hand, brief hot showers have shown itch-relieving effects in experimental studies applying heat to chronic pruritus and atopic skin (Yosipovitch, Duque et al. 2007, Pfab, Valet et al. 2010). Also, lukewarm baths with colloidal oatmeal may restore skin barrier and sooth pruritus (Lisante, Nuñez et al. 2017). Moisturisers with water and liquid paraffin base are used in soothing creams and emulsions. Several active ingredients are used in emollients suitable for dry skin. The effects of urea (5%–10%) and glycerol (20%) on pruritus are the best studied (Swanbeck and Rajka 1970, Breternitz, Kowatzki et al. 2008). Propylene glycol (20%) and lactic acid (1.5%–5%) may also contribute to hydration of the skin and to a reduction in pruritus (Lindh and Bradley 2015). In addition, propylene glycol and lactic acid have antimicrobial properties, making preservatives redundant. Another antipruritic agent with antimicrobial properties is potassium permanganate, which can be used as an active ingredient in baths.

Emollients containing N-palmitoylethanolamine (PEA) (0.3%), an endogenous lipid, have been shown to significantly improve skin barrier function (Yuan, Wang et al. 2014) and weak to moderate antipruritic and analgesic effects in experimentally induced pain, pruritus and erythema by topical application (Dvorak, Watkinson et al. 2003, Rukwied, Watkinson et al. 2003). In (non-vehicle controlled) clinical trials and case series, it proved to have antipruritic effects in CPG, AD, CKD-associated pruritus and PUO (Szepietowski, Szepietowski et al. 2005, Ständer, Reinhardt et al. 2006, Eberlein, Eicke et al. 2008), as well as analgesic effects in postherpetic neuralgia (Phan, Siepmann et al. 2010). In a monocentric, double-blind RCT of 60 patients with AD it was shown that the preservation and

loss of moisture (measured by transepidermal water loss) were greatly improved with a PEA containing cream compared to the vehicle (Yuan, Wang et al. 2014); however, a vehicle-controlled study with 100 subjects did not show any significant difference between the lotion with and without PEA (Visse, Blome et al. 2017). Thus a PEA-containing topical can be considered an emollient therapy. Allergenic compounds (e.g. fragrances or preservatives) and irritant substances (e.g. surfactants) in emollients should be avoided.

Prior to further symptomatic therapy, the patient should undergo a careful diagnostic evaluation, as well as treatment for any underlying disease (Fig. 1, Tables 3 and 4). Pharmacologic interventions for specific pruritic diseases, e. g. AD and urticaria, should be performed according to the current guideline of the specific disease and the field's Cochrane Group (Zuberbier, Bindslev-Jensen et al. 2006, EASL 2009, Zuberbier, Aberer et al. 2014, Wollenberg, Oranje et al. 2016, Salavastru, Chosidow et al. 2017, Wollenberg, Barbarot et al. 2018, Wollenberg, Barbarot et al. 2018, Zuberbier, Aberer et al. 2018).

If pruritus continues to persist, consecutive or combined step-by-step symptomatic treatment is necessary (Table 11). Before considering systemic treatment, patient adherence to topical treatment, including skin care, needs to be ensured (Simon and Bieber 2014). Severe generalised CP often requires multiple treatment approaches, which may be administered alone or in different combinations and sometimes repeated. Some therapies are not approved for CP and can only be prescribed "off-label", which requires separate informed consent.

Expert recommendation: We recommend the use of moisturisers and emollients depending on the status of the skin.

6.2 Causative therapy and aetiology-specific treatment

CP can be addressed by treating the underlying disease, e.g. specific treatments for 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 PBC has received a transplant. For some underlying diseases, specific treatments have proven to be successful in relieving pruritus, even if the underlying disease is not

treated. Aetiology-specific treatments act on a known or hypothetically assumed pathogenesis of pruritus in underlying diseases. Evidence of efficacy can be found in controlled studies for only a few of these treatments. Treatments for CP in specific diseases are presented in Tables 7–11. 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 age.

6.3 Topical therapy

6.3.1 Local anaesthetics

Local anaesthetics (LA) are a heterogeneous group of compounds, e.g. benzocaine, lidocaine and polidocanol. They act via different groups of skin receptors, interfering with peripheral neural transmission of pruritus. Topical LA are widely used for the symptomatic treatment of localised forms of CP, such as neuropathic pruritus, CKD-associated pruritus, post-burn pruritus and paraneoplastic pruritus, as well as in the palliative care setting (Kopecky, Jacobson et al. 2001).

In experimental studies, LA exhibited only limited antipruritic effects in both histamine- and cowhage-induced pruritus, with short-term duration (10 min) after topical application (Weisshaar, Forster et al. 1997, Bauer, Schwameis et al. 2015). Successful use in the treatment of localised forms of pruritus such as notalgia paraesthetica has been reported in case series (Layton and Cotterill 1991, Weisshaar, Heyer et al. 1996).

Polidocanol, an anionic surfactant with local anaesthetic properties, selectively reduces cowhage-induced pruritus via PAR-2 inhibition (Hawro, Fluhr et al. 2014). It is commonly used in different galenic formulations, alone (polidocanol 2%–10%) or in combination with other active substances (urea) to treat larger skin areas, i.e. atopic skin.

Topical 1% pramoxine hydrochloride has been shown to ameliorate CKD-associated pruritus in a double-blind, placebo-controlled study and can be used to treat larger skin areas, also in combination with other antipruritic compounds (lactic acid, hydrocortisone) (Young, Patel et al. 2009).

Ethyl chloride spray, a topical cooling and anaesthetic agent, reportedly reduces histamine-induced itch in experimental studies and finds limited application in localised pruritus secondary to allergy skin testing (Gal-Oz, Rogowski et al. 2010).
Expert recommendation: We suggest the application of topical anaesthetics for localised pruritus including polidocanol for selected cases of generalised pruritus.

6.3.2 Zinc, menthol and camphor

Although zinc oxide has been used in dermatology for over 100 years due to its anti-inflammatory, antiseptic and antipruritic properties and its safety, there is only scarce literature on its effects. Prescriptions of zinc are frequent, with concentrations varying from 10%–50% in creams, liniments, lotions, ointments and pastes that are useful in the treatment of pruritus, especially localised forms of pruritus, in children as well as in adults (Welsh 1955). Calamine, which is often found in cooling liniments, contains 98% zinc oxide (Welsh 1955). In an experimental study zinc oxide was shown to be as effective as moderate potency corticosteroid in suppressing contact dermatitis (Wallengren 2011).
Menthol is an alcohol obtained from mint oils, or prepared synthetically. Applied to the skin and mucous membranes, it causes a sensation of coldness, followed by an analgesic effect (Welsh 1955). Menthol is used in dusting powders, liniments, lotions and ointments in concentrations from 1% to 10% (Welsh 1955). It has been shown to have a cooling effect for up to 70 min and to act as a counter-irritant (Yosipovitch, Szolar et al. 1996). Menthol binds to the TRPM8 receptor (Green and Schoen 2007), which belongs to the same TRP family of excitatory ion channels as TRPV1, the capsaicin receptor. These two receptors have been shown to occasionally co-exist in the same primary afferent neurons and promote thermo-sensations at a wide range of temperatures, 8–28°C and >42ºC, respectively (Green and Schoen 2007). First studies showed that topicals containing the TRPM8 agonist combination or menthoxypropanediol ameliorate CP (Ständer, Augustin et al. 2017, Misery, Santerre et al. 2018).
Camphor, an essential oil-containing terpene, is soluble in alcohol (Welsh 1955). Applied to the skin, it causes a sensation of warmth followed by a mild degree of anaesthesia (Welsh 1955). Camphor has been used in dermatology for decades in liniments, lotions and ointments at concentrations ranging from 2% to 20%. It has been shown to specifically activate another constituent of the TRP ion channel family, namely TRPV3 (Macpherson, Hwang et al. 2006). Camphor was recently

demonstrated to activate the capsaicin receptor, TRPV1, while menthol also activates the camphor receptor, TRPV3. These findings illustrate the complexity of sensory perception and explain the efficacy of ointments containing both menthol and camphor (Welsh 1955).

Expert recommendation: We recommend topical application of menthol and its derivates. We suggest topical application of camphor or zinc.

6.3.3 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 that induce dose-dependent erythema and burning. After repeated applications of capsaicin, the burning fades due to tachyphylaxis and retraction of epidermal nerve fibres (Szolcsanyi 2004). However, pruritus recurs some weeks following discontinuation of therapy, indicating no permanent degeneration of the nerve fibres (Wallengren and Hakanson 1992).

The greater the initial dose of capsaicin and the more frequent the applications, the sooner desensitization will appear and pruritus will disappear. The burning sensation accompanying topical treatment may be reduced by lidocaine or cooling of the skin (Knolle, Zadrazil et al. 2013, Misery, Erfan et al. 2015, Zeidler, Lüling et al. 2015). Unusual adverse effects include cough or sneezing due to inhalation of capsaicin from the skin or from the jar, as well as its effect on sensory nerve fibres in the mucous membranes (Szolcsanyi 2004). A lower concentration of capsaicin and less frequent applications will induce tachyphylaxis later, but may ensure better compliance. The concentration of capsaicin varies in different studies, but 0.025% capsaicin is well tolerated by most patients. If capsaicin is not available in this concentration as a standard drug, it can be produced using a lipophilic vehicle. Capsaicin is also readily soluble in alcohol (0.025% capsaicin in spir dil) suitable to treat burning scalp. A weaker concentration of 0.006% capsaicin is recommended for intertriginous skin, e.g. pruritus ani (Lysy, Sistiery-Ittah et al. 2003). High dose capsaicin treatment (8% patch) for neuropathic pruritus induced CP relief for up to 12 weeks and longer (Wagner, Roth-Daniek et al. 2012).

Topical capsaicin's effects have been confirmed in controlled clinical trials 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, Stolz et al. 1994, Reimann, Luger et al. 2000), prurigo nodularis (Hoogenberg, Tupker et al. 1992, Tupker, Coenraads et al. 1992, Reimann, Luger et al. 2000, Ständer, 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 psoralen and ultraviolet A (PUVA)-associated pruritus (Kirby and Rogers 1997). High-concentration topical capsaicin for the treatment of postherpetic neuralgia and HIV neuropathy have been evaluated in a Cochrane review (Derry, Sven-Rice et al. 2013).

Expert recommendation: We suggest topical capsaicin for localized forms of CP.

6.3.4 Topical glucocorticosteroids

Topical glucocorticosteroids are the first line therapy for inflammatory dermatoses and the antipruritic effect they display has been attributed to an indirect consequence of their anti-inflammatory properties. Thus they are not currently recommended for the treatment of pruritus in the absence of a skin disease. Once- or twice-daily application of a medium or high potency glucocorticosteroid to the trunk and extremities or a low potency preparation on the face or intertriginous areas for approximately 1–3 weeks is recommended in the case of pruritic dermatoses (Elmariah and Lerner 2011). Prolonged use and application to large areas is to be avoided. Children, pregnant women and elderly patients are especially susceptible to the adverse effects of glucocorticosteroids and should be closely monitored (Patel and Yosipovitch 2010, Chi, Kirtschig et al. 2017).

Some recent data hint at the possibility of an alternative mode of antipruritic action of glucocorticosteroids. Pruritus experimentally induced by histamine was significantly suppressed by topical hydrocortisone when compared to placebo (Zhai, Frisch et al. 2000). In another experimental model itch relief from nickel allergy provided by methylprednisolone aceponate was very rapid and preceded resolution of all other eczema findings, suggesting a direct antipruritic effect of the agent rather than just an indirect anti-inflammatory one (Curto, Carnero et al. 2014).

Some studies suggest that topical corticosteroids such as betamethasone valerate are effective in CNPG (Saraceno, Chiricozzi et al. 2010, Siepmann, Lotts et al. 2013). Intralesional application in single nodules of CPG may be considered but there are no studies verifying the efficacy of this therapy.

Expert recommendation: We recommend application of topical glucocorticosteroids in CP associated with inflammatory dermatoses and CPG. We recommend against topical glucocorticosteroids in CP on non-inflamed skin. We recommend against long-term treatment with topical glucocorticosteroids.

6.3.5 Tacrolimus and pimecrolimus

The effects of the topical calcineurin inhibitors (TCIs) tacrolimus and pimecrolimus on pruritus are mediated both through their immunological and their neuronal properties (Ständer and Luger 2003). Paradoxically, while they can induce transient pruritus at the beginning of treatment, in the medium-term they may provide an alternative treatment for many causes of pruritus. An initial burning sensation upon application, which may be due to activation of TRPV1, can be a biomarker of antipruritic effect on individual patients with CP (Leslie, Greaves et al. 2015). TCIs are highly effective against pruritus in AD, and do not have the atrophying effects of topical corticosteroids on the skin (Fleischer and Boguniewicz 2010, Wollenberg, Oranje et al. 2016). Furthermore, 0.1% tacrolimus ointment is more effective at reducing symptoms of AD when compared with low-potency corticosteroids, 0.03% tacrolimus and 1% pimecrolimus cream (Cury Martins, Martins et al. 2015). Clinical trials have shown benefit of both pimecrolimus and tacrolimus in seborrhoeic dermatitis, genital lichen sclerosus, intertriginous psoriasis and cutaneous lupus erythematosus and—only for tacrolimus—in resistant pruritus ani (Simpson and Noble 2005, Wollina, Hansel et al. 2006, Kalb, Bagel et al. 2009, Chi, Kirtschig et al. 2011, Kuhn, Gensch et al. 2011, Papp, Papp et al. 2011, Ang-Tiu, Meghrajani et al. 2012, Avgerinou, Papafragkaki et al. 2012, Suys 2012). Both substances can be used to treat localised forms of CP such as genital pruritus (Ständer, Schürmeyer-Horst et al. 2006). In other diseases, the available data are limited to small case series, or individual cases, e.g. hand eczema (pimecrolimus), rosacea (tacrolimus), graft-versus-host disease (tacrolimus), vulval pruritus (tacrolimus) or Netherton's syndrome (tacrolimus, pimecrolimus). Topical tacrolimus has been shown anecdotally to be effective in

pruritus associated with systemic diseases such as PBC (Aguilar-Bernier, Bassas-Vila et al. 2005) and chronic renal insufficiency (Pauli-Magnus, Klumpp et al. 2000, Kuypers, Claes et al. 2004). Despite early reports of efficacy of tacrolimus on CKD-associated pruritus, these observations have not been confirmed in a controlled study and so it is not recommended in these patients, although it may have some benefit in combination with systemic therapies (e.g. nalfurafine) (Duque, Yosipovitch et al. 2005, Ghorbani, Feily et al. 2011, Mettang 2016).

Numerous clinical trials have demonstrated the safety of using TCIs routinely, in children as well as adults (Cury Martins, Martins et al. 2015, Luger, Boguniewicz et al. 2015). The transient burning upon application diminishes after 5–10 days of regular (e.g. twice-daily) application in most cases (Bornhövd, Burgdorf et al. 2001). Some patients may experience flushing upon taking alcohol; however, this can be blocked with acetylsalicylic acid (500 mg) taken in advance of drinking alcohol (Wollenberg, Oranje et al. 2016). Long-term studies are required to assess the risk of lymphoma in both adult and paediatric patients using TCIs; however, this seems to be extremely rare (Siegfried, Jaworski et al. 2013). In the elderly population TCIs are recommended for inflammatory skin diseases and, if effective, can be used indefinitely (Leslie 2016).

Expert recommendation: We suggest tacrolimus and pimecrolimus for the treatment of localized forms of CP.

6.3.6 Acetylsalicylic acid

Topical acetylsalicylic acid (acetylsalicylic acid/dichlormethane solution) has been described to have antipruritic effects in occasional patients with lichen simplex and CPG (Yosipovitch, Sugeng et al. 2001, Katagiri 2016). However, this beneficial effect could not be confirmed in experimentally induced itch with histamine (Thomsen, Benfeldt et al. 2002).

Expert recommendation: We cannot make a recommendation with respect to topical acetylsalicylic acid for the treatment of CP.

6.3.7 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).

6.3.8 Topical mast cell inhibitors

Pruritus in AD responds to topical sodium cromoglycate (Haider 1977), which was confirmed by a placebo-controlled study (Stainer, Matthews et al. 2005). Comparison with vehicle showed that topical sodium cromoglycate (especially 4%) was effective in histamine-induced itch (Vieira Dos Santos, Magerl et al. 2010).

Expert recommendation: We suggest against the use of topical mast cell inhibitors for the treatment of CP.

6.4 Systemic therapy

6.4.1 Antihistamines

Antihistamines are the most widely used systemic antipruritic drugs in dermatology (Leslie 2013). Drugs that target the H1 receptor can effectively block the acute itch of cutaneous conditions as urticaria or insect bites, among others (Thurmond, Kazerouni et al. 2015).

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. Hydroxizine is the most commonly used first-generation antihistamine showing sedative, anxiolytic and antipruritic activities. In adult patients it is recommended as an antipruritic agent at a dosage of 25 mg at night, increasing to 25 mg three to four times a day if necessary. In children under 6 years the effective dose is up to 50 mg/day in divided doses, and 50–100 mg/day in children aged 6–12 years (Leslie 2015). However, the sedative effect of such antihistamines induce impaired sleep, interfering with the REM phase. A prospective cohort study recently suggested that its cumulative long-term use (and other cholinergic drugs) is associated with increased risk of dementia (Gray, Anderson et al. 2015). Increased drowsiness may be problematic in the elderly (Leslie 2016). Due to these side effects, the use of sedative antihistamines is nowadays limited, and the dose modified accordingly, especially in vulnerable populations (Leslie and Grattan 2017).

Second-generation antihistamines such as cetirizine, levocetirizine, loratadine, desloratadine, ebastine, fexofenadine, rupatadine or bilastine 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). For the treatment of PUO, loratadine (10 mg), fexofenadine (180 mg) or cetirizine (10 mg) are helpful. Cetirizine may be preferred for its mild sedative properties (Millington, Collins et al. 2018). Oral cetirizine has been shown to be preferable in CP to narrowband (NB) ultraviolet B (UVB) phototherapy, for reasons of cost-effectiveness and time-saving (Gokdemir and Doruk 2011).

In general, the non-sedative H1-receptor antagonists offer an effective reduction of CP in diseases associated with increased mast cell degranulation such as urticaria or mastocytosis (Sharma, Bennett et al. 2014). Rupatadine, a dual inhibitor of histamine H1 and PAF receptors, has been shown to significantly reduce the severity of pruritus in mastocytosis, as well as mosquito bite allergy and urticaria in both adults and children (Mullol, Bousquet et al. 2015). In adult patients with confirmed mosquito-bite allergy, rupatadine 10 mg administered prophylactically has been shown to be effective in reducing subsequent wealing and skin pruritus (Karppinen, Brummer-Korvenkontio et al. 2012). The newest antihistamine, bilastine, is highly selective for the H1 receptor. With properties of rapid onset, prolonged duration of action, no need for dose adjustment, and low potential for central nervous system (CNS) impairment or drug–drug interaction, bilastine is a front runner among other second-generation antihistamines in the management of chronic urticaria (Wang, Lim-Jurado et al. 2016). European guidelines on urticaria (Zuberbier, Aberer et al. 2018) recommend second-generation anti H1-antihistamines as the first-line therapy for chronic spontaneous urticaria, starting at licensed doses and being increased to up to four times the dose if licensed doses fail to control the disease. Systemic H1-antihistamines are often employed to treat pruritus in AD. The older, sedating H1-antihistamines may be more useful for this indication especially in acute AD flares, improving sleep quality in the short term, although these are not recommended for long-term use in children (Wollenberg, Oranje et al. 2016). The European guideline on AD does not recommend the general use of any antihistamines for AD, since there is no high-level evidence that non-sedating antihistamines reduce itch in AD, or that sedating antihistamines

are of benefit, except for aiding sleep (Apfelbacher, van Zuuren et al. 2013, He, Feldman et al. 2018).

It is currently thought that pruritus in psoriasis is also not histamine-mediated, and therefore antihistamines are not routinely recommended (Thurmond, Kazerouni et al. 2015). Recently, however, both sedating and non-sedating antihistamines have been shown to be moderately effective in reducing itch in patients with psoriasis, but further studies are needed on larger patient groups (Domagala, Szepietowski et al. 2017).

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

Antihistamines have been shown to be safe in specific populations. However, while there is no particular antihistamine that is universally effective for the treatment of pruritus, certain antihistamines [e.g. loratadine, cetirizine or rupatadine (Potter, Mitha et al. 2016)] are thought to be safer for use in children, pregnancy and lactation, and so may be preferred in these patients (Leslie, Greaves et al. 2015). The use of first-generation antihistamines is to be avoided in pregnant women (Gonzalez-Estrada and Geraci 2016). For the paediatric management of pruritus, long-term use of first-generation antihistamines is not recommended (Zuberbier, Aberer et al. 2014, Wollenberg, Oranje et al. 2016). The associated psychomotor impairment may impact the education and safety of children, and remains even while the child becomes used to the sedating effects (Powell, Leech et al. 2015). Second-generation antihistamines with appropriate dose adjustment are the first-line therapy for chronic urticaria in children (Belloni Fortina and Fontana 2014).

Although identified in human skin, H2-receptors play a minor role in pruritus, and H2-receptor antagonists alone have no antipruritic effect (Paul and Bodeker 1986, Hoare, Li Wan Po et al. 2000). A combination of H2-antihistamines and H1-antihistamines has been used in the treatment of pruritus in small trials, but the results are conflicting (Paul and Bodeker 1986, Hoare, Li Wan Po et al. 2000). It has recently been found that H3- and H4-histamine receptors are involved in pruritus, with the H4 in particular being associated with mast cell function, as well

as T cells, dendritic cells, monocytes and eosinophils (Tey and Yosipovitch 2011). The efficacy of an H4 receptor antagonist is currently under research in clinical studies and may be available as an antipruritic therapy in the near future (Engelhardt, Smits et al. 2009). There is pre-clinical evidence that local antagonism of the H3 receptor can induce scratching; therefore, new drugs that target the H3R are anticipated in the field, with the hope that more effective treatment of chronic pruritus can be offered to patients in the future (Thurmond 2015).

A case series suggests that updosing of antihistamines may also be beneficial in CP (Schulz, Metz et al. 2009).

Expert recommendation: We recommend treating CP in urticaria with non-sedating H1-antihistamines. We suggest non-sedating H1-antihistamines in CP in mastocytosis. We suggest non-sedating and/or sedating H1-antihistamines as an initial symptomatic therapy of CP.

6.4.2 Mast cell inhibitors

Ketotifen (1 mg twice daily), showed antipruritic effects in patients with CKD-associated pruritus, but less than gabapentin (Amirkhanlou, Rashedi et al. 2016). Cromolyn sodium and placebo were compared in 62 haemodialysis patients and a significant decrease in itch was seen in the treatment group, but without effects on tryptase level (Vessal, Sagheb et al. 2010).

Expert recommendation: We suggest against the use of systemic mast cell inhibitors for the treatment of CP.

6.4.3 Glucocorticosteroids

Systemic glucocorticoids (GCs) are commonly used to treat severe CP associated with inflammatory skin disease or systemic disease, supported only by limited clinical evidence. In clinical experience, pruritus ceases within approximately 30 min of i.v. glucocorticosteroids in the treatment of urticaria or drug-induced exanthema. Likewise, in AD, allergic contact dermatitis, dyshidrosis and bullous pemphigoid a rapid reduction in pruritus is observed, which can be explained by their high anti-inflammatory potency. 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 in inflammatory skin diseases; however, they

should not be used for a period of more than 2 weeks (Streit, Von Felbert et al. 2002) due to their severe side-effects.

Severe, intractable lymphoma-related paraneoplastic CP can be successfully treated with short courses of systemic GCs (Wang and Yosipovitch 2010). An improvement in cutaneous T-cell lymphoma-related pruritus via suppression of IL-31 production, which has been shown to correlate with pruritus severity, was reported using dexamethasone (Cedeno-Laurent, Singer et al. 2015, Nattkemper, Martinez-Escala et al. 2016).

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

Expert recommendation: We suggest systemic glucocorticoids as a short-term treatment in selected cases of refractory CP, especially in paraneoplastic pruritus and palliative care.

6.4.4 Opioid receptor agonists and antagonists

Experimental and clinical observations have demonstrated that pruritus can be evoked or intensified by endogenous or exogenous μ-opioids (Fjellner and Hagermark 1982). This phenomenon can be explained by activation of CNS opioid receptors, mainly μ-opioid receptors. Reversing this effect with μ-opioid antagonists thus leads to an inhibition of pruritus (Phan, Siepmann et al. 2010). The opposite is true for κ-opioids. Their binding to κ-opioid receptors leads to inhibition of pruritus (Phan, Lotts et al. 2012).

Several clinical studies have demonstrated that different μ-opioid receptor antagonists may significantly diminish pruritus (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. 2012). In double-blind RCT, μ-opioid receptor antagonists such as nalmefene, 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, Legroux-Crespel, Clèdes et al. 2004). Results were variable, ranging from significant reduction of pruritus to no response. Naltrexone (50 mg/d) was more effective than placebo on CP in patients with AD (Malekzad, Arbabi et al. 2009). Case reports have demonstrated efficacy of naltrexone in several pruritic dermatoses.

Nalfurafine, a preferential κ-opioid receptor agonist, was investigated in CKD-associated CP in two large RTCs (Wikstrom, Gellert et al. 2005, Kumagai, Ebata et al. 2010). Both trials demonstrated significant clinical benefit of nalfurafine in patients with CKD-associated pruritus (Phan, Lotts et al. 2012) within the first 7 days of treatment. Similar outcomes in terms of results and adverse drug effects were obtained in an open-label long-term study with 5 mg nalfurafine given orally in 211 haemodialysis patients over a period of 52 weeks (Kumagai, Ebata et al. 2012). In a RCT on 318 patients with refractory cholestatic pruritus nalfurafine (2.5 and 5.0 mg given orally per day) reduced itch significantly more than placebo as measured on a VAS scale (28.56 and 27.46 vs. 19.25) (Kumada, Miyakawa et al. 2016). The drug is currently licensed only in Japan.

Expert recommendation: We suggest mu-opioid receptor antagonists in refractory CP, especially in cholestatic pruritus.

6.4.5 Gabapentin and pregabalin

Gabapentin is an antiepileptic and anxiolytic drug also used in neuropathic pain and 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 with paroxysmal pain or pruritus. Pilot studies have been performed for the treatment of pruritus caused by burns and wound healing in children demonstrating antipruritic effects of gabapentin (Mendham 2004). Double-blind RCTs were performed for CKD-associated pruritus (300 mg thrice weekly or 400 mg twice weekly after haemodialysis sessions) (Gunal, Ozalp et al. 2004, Naini, Harandi et al. 2007) and cholestatic pruritus (Bergasa, McGee et al. 2006). Gabapentin was safe and

effective for treating CKD-associated pruritus (Vila, Gommer et al. 2008, Razeghi, Eskandari et al. 2009). It was shown to be effective in six cases of brachioradial pruritus, but more disappointing in notalgia paraesthetica (Kanitakis 2006, Matsuda, Sharma et al. 2016). An anecdotal indication is cutaneous T-cell lymphoma (Demierre and Taverna 2006).

Pregabalin is similar to gabapentin and a more recent drug. Its use has been suggested in a case of cetuximab-related pruritus, aquagenic pruritus and in CKD patients unable to tolerate gabapentin (Porzio, Aielli et al. 2006, Ehrchen and Stander 2008, Rayner, Baharani et al. 2012). A controlled trial demonstrated a significant antipruritic effect of pregabalin in patients on haemodialysis within 1 month (Aperis, Paliouras et al. 2010). In another study on uremic itch, treatment with 75 mg of pregabalin given orally twice weekly in dialysis-dependent patients was compared either to ondansetron or placebo. While a significant effect of pregabalin could be documented, the use of ondansetron and placebo did not yield significant results (Yue, Jiao et al. 2015). In an open study 30 patients with CNPG were treated with 75 mg pregabalin per day orally. Treatment improved itch in 76% of patients after a 3-month treatment course (Mazza, Guerriero et al. 2013). Pregabalin 50 mg every other day or 10 mg doxepin given daily for 4 weeks in patients with CKD-associated pruritus led to a significant improvement of pruritus in both groups, but was significantly more effective in patients receiving pregabalin (Foroutan, Etminan et al. 2017).

However, regarding the use of gabapentin or pregabalin. an analysis by the US Renal Data System on a large cohort issued a caveat to the use of these drugs. Their use was associated with much higher hazards of altered mental status, falls and fractures (Ishida, McCulloch et al. 2018).

Expert recommendation: We recommend gabapentin and pregabalin in neuropathic CP and in CKD-associated pruritus. We suggest gabapentin and pregabalin for refractory CP and PUO.

6.4.6 Antidepressants

Recent systematic reviews demonstrate evidence that antidepressants are effective particularly in refractory pruritus, pruritus in CKD, cholestasis or neoplasm (Kouwenhoven, van de Kerkhof et al. 2017), as well as in other forms of CP (Brasileiro, Dayanna Patrícia de Carvalho Barreto et al. 2016, Kaur and Sinha 2018). Psycho-emotional factors are known to modulate the "itch threshold"

(Schut, Grossmann et al. 2015). 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) and have a clear correlation (Wang, Yang et al. 2018). Antidepressants probably also exert an effect on pruritus through their pharmacological action on serotonin and histamine (Kouwenhoven, van de Kerkhof et al. 2017).

The antipruritic action of serotonin reuptake inhibitors (SSRIs) does not start until after 2–3 weeks and the maximum effect is usually seen at 4–6 weeks after initiation of therapy (Szepietowski and Reszke 2016); only escitalopram 10–40 mg/day might have a slightly shorter efficacy period. SSRIs such as paroxetine can have an antipruritic effect on patients with PV, psychogenic or paraneoplastic pruritus and other patients with chronic PUO (Zylicz, Krajnik et al. 2003, Heisig, Salomon et al. 2012). Paroxetine (20 mg/d) has exhibited antipruritic effects in pruritus due to PV (Tefferi and Fonseca 2002), paraneoplastic pruritus (Zylicz, Smits et al. 1998, Weisshaar 2008) and psychiatric disease (Biondi, Arcangeli et al. 2000, Heisig, Salomon et al. 2012). In two patients pruritus was induced by discontinuation of paroxetine treatment for depression (Mazzatenta, Peonia et al. 2004). An 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 CP of dermatological origin reported a significant antipruritic effect (Ständer, Bockenholt et al. 2009). Sertraline proved effective in cholestatic pruritus both in adults (Mayo, Handem et al. 2007) and children (Thébaut, Habes et al. 2016), as well as in CKD-associated pruritus (Shakiba, Sanadgol et al. 2012, Chan, Li et al. 2013). In a recent double-blind RCT among 50 haemodialysis patients, sertraline was shown to be effective in reducing uremic pruritus (Pakfetrat, Malekmakan et al. 2018), while Doxepin also showed positive effects in seven patients (Foroutan, Etminan et al. 2017). Doxepin may be administered in a dose from 25–50 mg/day.

Tricyclic antidepressants like doxepin (Shohrati, Tajik et al. 2007) have been effective in urticaria, AD, cutaneous T-cell lymphoma, carcinoma en cuirasse and HIV-related pruritus. It shows almost identical effects compared with hydroxyzine (Shohrati, Tajik et al. 2007). Amitriptyline 25 mg/day has shown a reduction in pruritus in patients with brachioradial pruritus. Trimeprazine and trimipramine are

older antidepressants that exhibit some antipruritic effects in AD (Savin, Paterson et al. 1979).

Mirtazapine 15–45 mg/ day is an atypical antidepressant, both noradrenergic and serotonergic, and has been shown to be effective in the treatment of CP (Davis, Frandsen et al. 2003, Demierre and Taverna 2006, Lee, Girouard et al. 2016). In brachioradial pruritus antidepressants showed moderate effects to decrease pruritus (Wachholz, Masuda et al. 2017).

Side effects of antidepressants are common and include drowsiness, fatigue and headache, mostly initially, but also cardiovascular and gastrointestinal symptoms occur; therefore, caution should be shown in elderly patients (Kouwenhoven, van de Kerkhof et al. 2017). Recommended treatment doses for pruritus in malignant diseases are paroxetine 20–40 mg/day or mirtazapine 15–30 mg/day; for patients with cholestasis or CKD amitriptyline 25–50 mg/day or doxepin 25–20 mg/day.

Expert recommendation: We recommend selected antidepressants (e.g. paroxetine, mirtazapine, doxepin, amitryptiline) for psychogenic CP and for refractory CP, especially in malignant, cholestatic and chronic kidney disease.

6.4.7 Serotonin receptor antagonists

Due to the pathophysiological significance of serotonin in various diseases, e.g. kidney and liver diseases, serotonin receptor antagonists (of the 5-HT3 type) such as ondansetron (8 mg 1–3x/day), topisetron (5 mg/day) and granisetron (1 mg/day) have been used anecdotally to treat pruritus(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 controlled studies 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 controlled studies (Ashmore, Jones et al. 2000, Murphy, Reaich et al. 2003, Weisshaar, Dunker et al. 2004).

Expert recommendation: We recommend against serotonin receptor antagonists in the treatment of CP.

6.4.8 *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 antagonism of tumour necrosis factor-α (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 in pruritus on thalidomide (50–300 mg/day) (Winkelmann, Connolly et al. 1984, Johnke and Zachariae 1993). In a very recent review the authors refer to how patients were started on higher doses of 200 mg or more daily in earlier studies (Lim, Maranda et al. 2016). In the majority of studies since then, however, patients received an initial dose ranging from 50 to 200 mg/day, following which the dosage was tailored according to response or the development of side effects. A prospective open trial of thalidomide 100 mg/day, followed by NB-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 randomised, 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/day) (Gaspari 2002). In most cases the peripheral neuropathy is reversible (Lim, Maranda et al. 2016). Thalidomide could be considered particularly in a palliative setting (Lowney, McAleer et al. 2014)

The scarce information on lenalidomide, a more potent analogue of thalidomide, seems promising (Kanavy, Bahner et al. 2012). More studies are needed to evaluate the effectiveness and tolerability of this analogue of thalidomide.

Expert recommendation: We suggest thalidomide for selected cases of refractory CP after informing the patient about teratogenicity and dose-related risk of neuropathy.

6.4.9 *Leukotriene receptor antagonists and TNFα antagonists*

Leukotriene receptor antagonists (e. g. montelukast) and TNFα antagonists influence the pathogenesis of AD. They have been used in combination with antihistamines as antipruritic therapy. Montelukast has also been used in several types of urticaria as well as in combination with antihistamines. A combination of

H1-antihistamine with a leukotriene antagonist has been reported to alleviate pruritus in chronic urticaria (Daly and Shuster 2000).

Expert recommendation: We suggest against leukotriene receptor antagonists in the treatment of CP.

6.4.10 *Cyclosporine, methotrexate, azathioprine and tacrolimus*

Controlled clinical studies investigating the efficacy of systemic anti-inflammatory drugs on CP are scarce. Cyclosporine is the only drug that has been approved for the treatment of pruritus in AD (Simon and Bieber 2014). The effect of methotrexate and azathioprine on pruritus is mainly documented in retrospective case reports. All these therapies are associated with significant systemic toxicity and require careful patient monitoring. The choice of systemic therapy for CP depends on comorbidities (existing or prior neoplasms or cardiovascular disease), blood tests (haematology, liver and kidney function), age and history of alcohol abuse.

Pruritus in AD responds to treatment with cyclosporine as demonstrated in several double-blind controlled studies (van Joost, Stolz et al. 1987, Wahlgren, Scheynius et al. 1990, Simon and Bieber 2014). Cyclosporine has also proved effective in pruritus associated with refractory chronic urticaria (Viegas, Ferreira et al. 2014). Cyclosporine has been administered in PN for 24–36 weeks, using doses of 3.0–4.5 mg/kg per day. Improvement was observed in both pruritus and skin lesions after 2 weeks of treatment (Berth-Jones, Smith et al. 1995, Siepmann, Luger et al. 2008). It seems likely that, in these diseases, cyclosporine acts on pruritus through its immunological effects. However, direct effects on nerve endings are also possible (Wallengren 2004). Successful use of cyclosporine in non-immunological disease was reported in several studies, e. g. 10 patients with pruritus of senescence were treated with cyclosporine 5 mg/kg per day for 8 weeks (Teofoli, De Pita et al. 1998). All patients in this uncontrolled, open study responded. Case reports describe antipruritic effects in dystrophic epidermolysis bullosa-associated CP (Calikoglu and Anadolu 2002).

Methotrexate, licensed for psoriasis, has proved effective for psoriasis-associated pruritus (Dawn and Yosipovitch 2006). Patients with severe AD refractory to topical therapy may respond to methotrexate with greatly reduced pruritus (Simon 2011, Simon and Bieber 2014). In a retrospective report on 13 patients with CNPG, 10 markedly improved on methotrexate at doses of 7.5–20 mg once

weekly for a minimum of 6 months (Spring, Gschwind et al. 2014). In a recent multicenter study, a 90% overall response rate was reported in 39 patients with difficult-to-treat prurigo using methotrexate with a median weekly dose of 15 mg (Klejtman, Beylot-Barry et al. 2018).

Azathioprine, licensed as a corticosteroid-sparing drug for blistering diseases, has proved effective in pruritus associated with bullous pemphigoid in doses of 50–200 mg/day (Kibsgaard, Bay et al. 2015). Patients with severe AD refractory to topical therapy may respond to azathioprine with greatly reduced pruritus (Simon 2011, Simon and Bieber 2014). In a retrospective review 96 patients with life-altering CP who had previously responded to systemic steroids were reported. A daily azathioprine dose ranging from 25 to 275 mg resulted in relief of pruritus with a reduction in VAS from 9.2 prior to treatment to 1.6 post treatment. The mean duration of therapy in this study was 53 months and 33% of the patients were forced to discontinue treatment due to adverse drug effects (Maley and Swerlick 2015).

Data on systemic treatment with tacrolimus in CP are sparse. Besides case reports (Halvorsen and Aasebø 2015), one open-label study on a sequential treatment with oral (6 weeks) and topical tacrolimus (11 weeks) in 12 patients with severe AD resulted in a substantial reduction in pruritus (Keaney, Bhutani et al. 2012). In contrast to these results, a case series in four patients with AD treated with 5 mg tacrolimus twice daily for 14 months showed poor results in three of the patients (Lee, Frankum et al. 2012).

Expert recommendation: We suggest cyclosporine, methotrexate and azathioprine for refractory CP associated with inflammatory dermatoses and CPG.

6.4.11 Neurokinin receptor 1 antagonist

Substance P (SP) plays a dominant role in pruritus induction after release from cutaneous sensory neurons. Via binding to the neurokinin 1 receptor (NK1R) on keratinocytes, blood vessels and mast cells, SP promotes inflammation and mast cell degranulation. Cutaneous SP levels are increased in conditions with hyperplasia of skin nerves (AD, PN). Accordingly, inhibition of the pruritogenic effects of SP by blocking the corresponding receptor may have antipruritic effects. Several case series and case reports suggest a positive role of the NK1R antagonist aprepitant in CP, e.g. cutaneous T-cell lymphoma, solid tumours, drug-induced pruritus, CP with atopic predisposition and CNPG (Ständer, Siepmann et

al. 2010, Vincenzi, Fratto et al. 2010, Vincenzi, Tonini et al. 2010, Booken, Heck et al. 2011, Torres, Fernandes et al. 2012, Ständer and Luger 2015). However, recent controlled trials including a randomized double-blind, placebo-controlled phase-II study using topical or systemic aprepitant failed to show a benefit compared to placebo (Lönndahl, Holst et al. 2018, Ohanyan, Schoepke et al. 2018, Tsianakas, Zeidler et al. 2018). Serlopitant is a novel NK1R antagonist that can be administered for long-term therapy. RCTs demonstrated a significant effect on pruritus of CPG and was well tolerated (Ständer, Kwon et al. 2018, Yosipovitch, Ständer et al. 2018).

Expert recommendation: We suggest NKR1 antagonists such as serlopitant in refractory CP and CPG.

6.4.12 Biologics

Biologic therapies have burst onto the armamentarium to treat CP in certain cutaneous diseases. In addition, some biologic approaches have been developed to control CP alone. This is the case with omalizumab for CSU. This humanized recombinant monoclonal antibody binds specifically to the Cε3 domain of the immunoglobulin E (IgE) heavy chain. Omalizumab reduces the levels of free IgE and the density of the high-affinity IgE receptor, both of which are essential in mast cell and basophil activation and consequently degranulation (McCormack 2014). Omalizumab was approved in 2014 in Europe (300 mg) and the US (150 and 300 mg), administered subcutaneously every 4 weeks for recalcitrant chronic spontaneous urticaria refractory to H1-antihistamines in adults and children (aged 12 years and above). The itch severity score was the primary endpoint assessed in the phase III clinical trials. Omalizumab showed effective and rapid reduction of itch in a dose-dependent manner that was maintained over the treatment period. An improvement in the number of hives, need for emergency medication and quality of life of patients with chronic spontaneous urticaria, as well as good tolerance and safety profiles, were also reported (Kaplan, Ledford et al. 2013, Maurer, Rosén et al. 2013, Saini, Bindslev-Jensen et al. 2015). A clinically relevant response is seen within a few weeks of initial administration. Side effects are usually mild or moderate and include mainly headache, nasopharyngitis, myalgia and local symptoms at the injection site.

With regard to AD, monoclonal antibodies that block signalling of both IL-4 and IL-13, key T helper cell 2 (Th2) cytokines, are in development. Dupilumab, a fully

human monoclonal antibody directed against the IL-4 receptor α (IL-4R α), has been shown to be efficient in controlling patients' assessment of CP as measured by the pruritus NRS score at week 16, with a significant reduction of pruritus seen as early as week 1 (dupilumab 300 mg once a week) in severe adult AD patients in the phase 2b trial (Thaci, Simpson et al. 2016). A number of trials are currently ongoing with different targets such as IL-31, IL-22, TSLP and CRTH.

Pruritus-reducing effects of biologic treatment on psoriatic pruritus have been reported (Papp, Reich et al. 2015, Paul, Cather et al. 2015, Kimball, Luger et al. 2016, Sobell, Foley et al. 2016, Strober, Sigurgeirsson et al. 2016, Gottlieb, Gordon et al. 2018, Kimball, Luger et al. 2018, Papp, Blauvelt et al. 2018, Thérénė, Brenaut et al. 2018). One single report of cases referred to persistent CP (Shibuya. T, Honma et al. 2018). Secukinumab significantly improved CP in a phase 3 study (Strober, Sigurgeirsson et al. 2016). Ixekizumab showed long-term effects on CP in psoriasis in a phase 3 clinical trial and maintenance therapy sustained improvements in psoriasis severity over more than 1 year (Kimball, Luger et al. 2016, Kimball, Luger et al. 2018). According to a systematic review anti-IL 17, JAK inhibitors, adalimumab, and apremilast are effective in reducing CP in psoriasis, with anti-IL-17 showing the largest effect in reducing psoriasis (Thérénė, Brenaut et al. 2018).

According to the different pathogenic mechanisms involved in pruritus, potential new monoclonal antibodies will be developed that, e.g. target Na V1.7, a voltage sensor for pain and itch relief (Lee, Park et al. 2014). However, these developments lie in the future.

Expert recommendation: We suggest omalizumab for refractory CP in CSU and dupilumab for refractory CP in AD. We cannot make a recommendation with respect to the use of monoclonal antibodies in CP of other origin.

6.4.13 Physical treatment modalities

Physical treatments such as transcutaneous electrical (field) stimulation and acupuncture have been described for the treatment of CP (Hettrick, O'Brien et al. 2004, Mohammad Ali, Hegab et al. 2015). Acupuncture is the oldest and best studied alternative option with evidence-based effect on pain, but much less evidence of its antipruritic effects. A few placebo-controlled experimental studies have shown that local treatment with acupuncture needling reduces histaminergic itch in healthy volunteers and allergen-induced itch in patients with AD (Belgrade,

Solomon et al. 1984, Lundeberg, Bondesson et al. 1987, Pfab, Huss-Marp et al. 2010). The effect of acupuncture on sensory innervation in the skin was investigated in 10 subjects that were treated with 10 acupuncture needles subcutaneously during twice-weekly 25-min sessions over 5 weeks and skin biopsies revealed reduced density of sensory nerve fibres (Carlsson and Wallengren 2010). In a retrospective study, symptomatic relief of neuropathic pruritus (brachioradial CP, notalgia paresthetica, meralgia paresthetica) in 12 of 16 patients treated with acupuncture was reported (Stellon 2002). Relapse occurred in 37% of patients within 1–12 months following treatment. In a placebo-controlled study of six patients with intractable pruritus in CKD, electrical needle stimulation at the point of the elbow reduced severity, frequency and distribution of itch both day and night (Stellon 2002), while control treatment with superficial electrical stimulation was ineffective. Che-Yi et al. randomised 40 patients with refractory uremic pruritus into two groups: acupuncture needling was applied either unilaterally at the acupoint of the elbow or at a non-acupoint (control). The patients were treated three times weekly for 1 month. At the end of the treatment period and at 3 months follow-up, only the acupoint group showed a 50% reduction in pruritus (Che-Yi, Wen et al. 2005). The rationale for the use of acupuncture in the treatment of itch, as well as its effects in uremic pruritus and allergic diseases has been reviewed (Carlsson and Wallengren 2010, Pfab, Schalock et al. 2014, Badiee Aval, Ravanshad et al. 2018).

A double-blind randomised placebo-controlled study in 30 patients with AD revealed that acupuncture achieved a significant reduction of itch (Pfab, Huss-Marp et al. 2010). In another study in 40 patients with refractory UP, an acupuncture needle was inserted at the Quchi acupoint and then removed after 1 h. Patients undergoing this treatment showed a substantial improvement in itch compared to controls (Che-Yi, Wen et al. 2005).

Transcutaneous electrical nerve stimulation (TENS), which activates electrically myelinated nerve fibres (α and δ), is widely used for the treatment of chronic pain (Gibson, Wand et al. 2017). Fjellner et al. studied the effect of TENS on CP of various origin in 41 patients for 5–47 days. Initially, TENS ameliorated pruritus in 63% of patients, but the effect declined over the course of therapy and was regarded as placebo (Fjellner and Hägermark 1978).

Another technique, cutaneous field stimulation (CFS), was developed to electrically stimulate unmyelinated C-fibres at the dermo-epidermal junction in order to treat pruritus (Nilsson, Levinsson et al. 1997). In an experimental study on 21 subjects, the pruritus induced by histamine iontophoresis was completely abolished by CFS (Nilsson, Levinsson et al. 1997). In a controlled study, 27 atopic patients with CP were treated with CFS and TENS (Nilsson, Psouni et al. 2004), CP was significantly surpressed for 7 h after cessation of CFS, but not after TENS. In an open trial on 19 patients (16 patients with neuropathic pruritus and three patients with generalized pruritus) using CFS once daily for 25 min for 5 weeks, pruritus was reduced by 49% at the end of treatment (Wallengren and Sundler 2001). Skin biopsies revealed a significant reduction in epidermal nerve fibres following the treatment (Wallengren and Sundler 2001). In this study, pruritus relapsed gradually after discontinuation of CFS, indicating nerve fibre regeneration in the epidermis.

Expert recommendation: We cannot make a recommendation with respect to physical treatment for the treatment of CP.

6.5 Ultraviolet phototherapy

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). Immunomodulatory effects due mostly to the release of anti-inflammatory neuropeptides, or the inhibition of pro-inflammatory mediators (e.g. IL-1, TNFα), make these different UV treatments particularly useful for treating pruritus associated with inflammatory dermatoses (Steinhoff, Cevikbas et al. 2011).

For the treatment of AD, phototherapy is a common and valid treatment, inhibiting pruritus by reducing numbers of nerve fibres in the epidermis and normalising the expression of axonal guidance molecules (e.g. nerve growth factor, semaphorin 3A) in atopic skin (Tominaga, Tengara et al. 2009, Kamata, Tominaga et al. 2016). Treatment with phototherapy can improve, or even resolve, AD with remission of up to 6 months and no reported serious adverse effects in the short-term (Wollenberg, Oranje et al. 2016). Preference is given to UVA-1 and NB-UVB as

modalities, since both have been found to be equally effective in improving pruritus of AD, although it is noted that NB-UVB has the dual advantage of less heat load and shorter duration of phototherapy (Majoie, Oldhoff et al. 2009, Garritsen, Brouwer et al. 2014). Systemic PUVA has also been shown to effectively treat the itch of AD, but with side effects including burning, pain, nausea, headache, erythema and lentigenes (Hong, Buddenkotte et al. 2011). A study comparing bath-PUVA with NB-UVB found both to be very effective measures, reporting that relief from pruritus was usually achieved in the first 2 weeks, and consistently preceded the resolution of skin lesions (Der-Petrossian, Seeber et al. 2000).

UVB laser may be still more effective than NB-UVB, with localised AD and associated pruritus being successfully treated with 308-nm xenon chloride excimer laser (Baltas, Csoma et al. 2006).

Both AD and lichen amyloidosis have been successfully treated by combinations of NV-UVB with steroids or cyclosporine A (Steinhoff, Cevikbas et al. 2011).

For the treatment of CPG, 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, solar, chronic and idiopathic urticaria, as well as urticaria pigmentosa and folliculitis of pregnancy (Rombold, Lobisch et al. 2008, Steinhoff, Cevikbas et al. 2011). 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, UVB-induced apoptosis of mast cells has been postulated to explain relief of pruritus (Szepietowski, Morita et al. 2002). Furthermore, phototherapy leads to a reduction in CGRP-immunoreactive nerve fibres in the skin (Wallengren and Sundler 2004). No further benefit has been found by adding UVA in combination with NB-UVB phototherapy for the treatment of pruritic inflammatory skin disease (Su, Xu et al. 2016). A novel treatment that has proven beneficial in pilot studies is a topical cream that filters solar UVB (Zanardelli, Kovacevic et al. 2016). This has the advantage of saving time, inconvenience and expense associated with traditional UV therapy.

Pruritus associated with mastocytosis can be treated with oral PUVA, although alleviation is only short-term, or with NB-UVB if PUVA is not tolerated (Grattan and Radia 2016).

UV phototherapy has been used with some success in conditions with pruritus on primarily non-inflamed or normal appearing skin. It has been particularly effective in many cases of CKD-associated pruritus (Saltzer and Grove 1975, Gilchrest, Rowe et al. 1977, Mettang 2016). 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 the reduction of CKD-associated pruritus (Seckin, Demircay et al. 2007). However, a later RCT failed to demonstrate a significant difference in the reduction of pruritus intensity in patients receiving NB-UVB compared with a control group (Ko, Yang et al. 2011). In another case NB-UVB treatment was unsuccessful, but BB-UVB helped (Hsu and Yang 2003). For end-stage renal disease BB-UVB is recommended at a frequency of three times per week, tapering to one or two maintenance sessions per week to achieve control of pruritus (Berger and Steinhoff 2011).

UV therapy has also been reported to be effective in a number of cases of pruritus associated with other systemic diseases, including hepatic and metabolic disorders, as well as malignancy (Leslie 2013). BB-UVB was found to reduce cholestatic-induced pruritus in 10/13 patients (Decock, Roelandts et al. 2012). In polycythemia vera, 8/10 patients responded to NB-UVB in an open study (Baldo, Sammarco et al. 2002). In a single case report a patient with Hodgkin's disease responded well to BB-UVB (Kaptanoglu and Oskay 2003).

Aquagenic pruritus showed response to bath-PUVA therapy (Jahn, von Kobyletzki et al. 1997) and systemic PUVA (Martinez-Escribano, Quecedo et al. 1997, Holme and Anstey 2001) for the duration of therapy. To treat aquagenic pruritus, PUVA was found to be superior to BB-UVB in five patients (Menage, Norris et al. 1993). Recently, two patients with aquagenic pruritus were reported to show a good, but transient 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). Phototherapy has been useful in treating idiopathic pruritus in some HIV patients, as well as HIV-associated dermatoses (Singh and Rudikoff 2003).

Common adverse effects of UVB phototherapy are tanning and erythema. Both UVA and UVB have been associated with skin ageing. The potential carcinogenic effect of phototherapy is of concern. In general, the use of UVB has shown no or little association with skin cancer and is considered a very safe treatment option (Lee, Koo et al. 2005, Hearn, Kerr et al. 2008). However, studies of PUVA-treated patients and associated cancer risk have reported increased incidence of melanoma (particularly squamous cell carcinoma) and recommend careful selection of patients with rigorous follow-up (Lindelof, Sigurgeirsson et al. 1999, Stern and Study 2001).

Expert recommendation: We suggest UVA and UVB (NB-UVB/BB-UVB) phototherapy for refractory CP in inflammatory skin diseases, cutaneous lymphoma CPG and selected cases of systemic pruritus (e.g. CKD-associated pruritus, cholestatic pruritus, aquagenic pruritus). We suggest UV phototherapy in combination with topical and/or systemic treatment, with the exception of calcineurin inhibitors and immunosuppressant drugs.

6.6 Treatment in special populations

6.6.1 Treatment of chronic pruritus in the elderly

Elderly patients with CP require special attention, even though the general principles of treatment apply. The older patient with CP characteristically presents a mixed clinical picture of comorbidities and polypharmacy, including physical and cognitive limitations; some degree of xerosis cutis is omnipresent in most cases (Berger, Shive et al. 2013, Valdes-Rodriguez, Stull et al. 2015, Leslie 2016). Any underlying condition such as CKD, hepatobiliary disease or malignancies should be addressed primarily (Valdes-Rodriguez, Stull et al. 2015). Treatment is therefore challenging and needs to be tailored to each case.

The application of topical soothing agents and, if required, anti-inflammatory treatment are recommended for the management of xerosis. Fingernails should be kept short and soap should be avoided or restricted to the axilla, groin, scalp and soles, preferably using acidic pH soap. Furthermore, less frequent bathing, preferably in tepid water, and the avoidance of astringents and lactic acid (>5%) are also recommended. The application of petroleum-containing moisturisers immediately after bathing is helpful. More aggressive hydration might be necessary: after a 20-min soak, an effective moisturiser is applied on patted-dry

skin, which is then covered with kitchen clingfilm (plastic wrap) or a moist garment. This technique is called the “soak and smear” method (Gutman, Kligman et al. 2005, Berger, Shive et al. 2013). Oatmeal baths can also be useful, likely due to the anti-inflammatory properties of oatmeal (Pazyar, Yaghoobi et al. 2012). Other topical treatments with urea solutions, menthol, pramoxine, pimecrolimus, tacrolimus and topical amitriptyline-ketamine with lidocaine can be beneficial; however, topical corticosteroids should be avoided on elderly skin due to skin thinness.

Systemic treatment of CP in an elderly patient demands special caution. Second-generation non-sedating antihistamines may be useful, but first-generation sedating antihistamines should be avoided, as well as tricyclic antidepressants such as doxepin due to anticholinergic effects. Long-term systemic steroids should also be avoided, since impaired immunity and comorbidities are often present in the elderly patient (Valdes-Rodriguez, Stull et al. 2015). The antiepileptic drugs gabapentin and pregabalin are useful, but dizziness and sedation may occur with increasing dose. In elderly patients, lower dosages of gabapentin and pregabalin are usually sufficient to control CP. The tetracyclic antidepressant mirtazapine can be effective against nocturnal itch (Lavery, Stull et al. 2016). SSRIs such as paroxetine and fluvoxamine are also effective in the elderly, but can exacerbate sexual dysfunction and insomnia (Valdes-Rodriguez, Stull et al. 2015). Sertraline is a good option for the treatment of cholestatic itch. The use of μ-opioid receptor antagonists and κ-opioid receptor agonists should be approached with caution as a result of hepatotoxicity, gastrointestinal symptoms and dizziness. Thalidomide might be a good option for the elderly patient with chronic itch (Valdes-Rodriguez, Stull et al. 2015). Successful use of cyclosporine was reported in several studies, e. g. 10 patients with pruritus of senescence were treated with cyclosporine 5 mg/kg per day for 8 weeks (Teofoli, De Pita et al. 1998).

UV phototherapy is an option in the elderly; however, caution must be taken in case of increased photosensitivity or phototoxicity caused by multiple drug ingestion (Leslie 2016). Overall, phototherapy such as NB-UVB (TL01) is a good treatment option, since it can avoid further polypharmacy; however, skin cancer needs to be borne in mind. Phototherapy in the elderly depends on the patient’s mobility. In summary, treatment of pruritus in the elderly is primarily focused on

efficient hydration of the skin. Caution should be shown with systemic therapy due to polypharmacy, interactions and adverse effects.

6.6.2 Treatment of chronic pruritus in pregnancy

Due to potential effects on the foetus, the treatment of pruritus in pregnancy requires prudent consideration of whether the severity of the underlying disease warrants treatment and careful selection of the safest treatments available. Topical corticosteroids are the most frequently used drugs for treating skin conditions and are prescribed to more than 6% of pregnant women (Chi, Wang et al. 2013). However, little is known about the effects of local corticosteroids on the foetus.

According to a very recent Cochrane review update, there are no causal associations between maternal exposure to topical corticosteroids of all potencies and pregnancy outcomes, including mode of delivery, congenital abnormalities, preterm delivery, fetal death and low Apgar score (Chi, Wang et al. 2015). A recent study showed a significantly increased risk of low birth weight in cases where more than 300 g of potent or very potent topical corticosteroids were applied over the course of the entire pregnancy (Chi, Wang et al. 2013). Systemic treatments such as systemic glucocorticosteroids, a limited number of antihistamines and UV phototherapy, e.g. UVA, may be necessary in severe and generalised forms of CP in pregnancy. UV phototherapy is a useful alternative therapy for pruritus during pregnancy that is refractory to steroids or antihistamines (Steinhoff, Cevikbas et al. 2011).

There is a lack of knowledge concerning the pharmacokinetics of the use of antihistamines during pregnancy. The use of first-generation antihistamines is to be avoided in pregnant women (Gonzalez-Estrada and Geraci 2016); on the other hand, they are also considered safe on the basis that they have already been prescribed for a very long time. Of the second-generation antihistamines, loratadine and cetirizine are the best studied (Treudler 2010). They can be prescribed after the first trimester in the case of well-considered indications. Administration immediately prior to or after birth must be avoided. NB as well as BB UVB phototherapy is safe; however, since folic acid levels may decrease with both (Murase, Heller et al. 2014), follow-up of folic acid levels is indicated. In summary, the treatment of pruritus in pregnancy is primarily focused on topical treatment in order to relieve CP, possibly complemented by UV phototherapy.

Caution should be shown with systemic therapy due to possible effects on the foetus.

6.6.3 Treatment of chronic pruritus in children

The management of CP in children is based on the diagnosed systemic or skin condition. Nevertheless. some general considerations must be taken into account once topical or systemic drugs are used, such as the body volume/body surface area rate and the total weight. In addition, the licensed age for any drug must be taken into account. Individualised management is recommended.

Topical treatments for pruritus should be focussed on the cause if possible. Avoidance of the specific and non-specific provocation factors is necessary. Such factors include, e.g.: inhalants, microbial agents, foods, textiles, chemicals and emotional stress. The use of emollients in an attempt to preserve barrier function is always required. Low- (class 1, 2) to medium-strength (class 3) glucocorticosteroids may be administered in children. Topical immunomodulators are used for AD and pruritus in children aged 2 years and older, but in some European countries pimecrolimus, for instance, is licensed for use in children older than 3 months. Topical capsaicin is not used in children <10 years. New topical active principles are in development for CP in children, such as a 4% cutaneous emulsion of sodium cromoglicate (Berth-Jones, Pollock et al. 2015) or a 2% topical ointment of crisaborole (phosphodiesterase-4 inhibitor) (Draelos, Stein Gold et al. 2016).

The dosages of systemic drugs need to be adjusted in children. The most common drugs used to control pruritus in AD and CSU in children is an H1-receptor inverse agonist. The common use of first-generation antihistamines (e.g. hydroxyzine dichlorhydrate) to avoid scratching during the night in AD has long been discussed based on the controversial role of histamine in dermatitis and on the defined adverse events, e.g. drowsiness and impaired attention. There is no mechanistic rationale for treating non-histaminergic pruritus-related AD with antihistamines (Metz, Wahn et al. 2013). The treatment of CSU in infants and children is based on the use of second-generation H1-antihistamines according to the same algorithm recommended for adults (Church, Weller et al. 2011, Zuberbier, Aberer et al. 2014). Cetirizine, desloratadine, fexofenadine, levocetirizine and loratadine have been studied in children and their long-term safety has been well established

in the paediatric population. Rupatadine has been recently approved for the treatment of CSU in children aged 2–11 years old based on a double-blind trial showing safe efficacy with respect to placebo at 1 mg/ml (Potter, Mitha et al. 2016). Certain antihistamines (e.g. loratadine, ceterizine) are thought to be safer for use in children, and thus may be preferred in these patients (Leslie, Greaves et al. 2015). In children aged under 6 years the effective dose of hydroxyzine is up to 50 mg/day in divided doses, and 50–100 mg/day in children aged 6–12 years (Leslie 2015). In summary, for the paediatric management of pruritus, long-term use of first-generation antihistamines is not recommended (Zuberbier, Aberer et al. 2014, Wollenberg, Oranje et al. 2016). The associated psychomotor impairment may impact the education and safety of children and persists even after the child has become accustomed to the sedating effects (Powell, Leech et al. 2015). Second-generation antihistamines with appropriate dose adjustment are first-line therapy for CP in children such as urticaria (Belloni Fortina and Fontana 2014).

Other therapies could also be considered, such as UV phototherapy, but the indication and protocol should be carefully considered together with the family due to possible long-term photo damage to the skin. A retrospective analysis of children up to the age of 18 years suffering from AD and psoriasis suggests NB-UVB treatment (Pavlovsky, Baum et al. 2011). In children, longer follow-up is essential to determine the true carcinogenic risk of UV therapy. An adjuvant psychological intervention as well as an educational approach can also be highly useful in children (Metz, Wahn et al. 2013).

Other systemic treatments such as cyclosporine are not licensed in children younger than 16 years due to a lack of clinical studies. They may be used in treatment-refractory cases (Weisshaar, Diepgen et al. 2005).

In summary, the treatment of pruritus in children is primarily focused on treatment of the skin disease, especially AD. Topical corticosteroids, topical immunomodulators and some antihistamines can be administered in children, but national regulations must be considered. UV phototherapy may be initiated depending on the child’s skin type and age. Caution should be shown with systemic therapy due to the lack of data and off-label use in children.

6.7 Psychosomatic therapy (relaxation techniques and psychotherapy)

The vicious itch–scratch cycle needs to be considered when a patient is treated for CP. The psychosomatic approach recognises the pruritus patient with regard to coping behaviour and possible stress attempts as cause or provocation factors in CP. Essentially, psychosomatic treatment could complement topical and systemic therapy and should be differentiated into unimodal psychological treatment and multimodal psychological treatment for CP (Evers, Schut et al. 2016). Depending on the factors involved, a unimodal (progressive muscular relaxation, autogenic training) or multimodal psychological approach is recommended (Evers, Schut et al. 2016). 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 CPG who might show unconscious automatic scratching behaviour.

Adjuvant psychosocial programmes focused on CP are most effective in AD (Gieler, Kupfer et al. 2000, Staab, von Rueden et al. 2002, Stangier, Ehlers et al. 2004, 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. There are more than 10 RCTs showing slightly beneficial effects; these were recommended for treatment by a Cochrane review on psychological interventions (Ersser, Cowdell et al. 2007). 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 CP of different aetiology (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). Internet-delivered (eHealth) self-management was investigated in recent years, mostly with cognitive behavioural interventions. Results demonstrate effects similar to face-to-face

psychotherapy (Van Beugen, Ferwerda et al. 2014). Studies specifically for dermatologic patients are promising (Bundy, Morawski et al. 2014)

Expert recommendation: We recommend educational programs. We suggest relaxation and habit reversal techniques as a complementary treatment for managing CP.

7 Key summary of discussion

- Chronic pruritus is frequent in medicine and needs a precise diagnostic work-up. Its management comprises treatment of the underlying disease, topical treatment modalities including symptomatic antipruritic treatment, UV phototherapy and systemic treatments.
- Sedative or non-sedating H1 antihistamines are suggested as an initial symptomatic therapy in severe CP and sleep loss. Studies on the systemic administration of higher doses of non-sedating antihistamines seem to be promising, but RCTs need to be conducted.
- Systemic glucocorticosteroids are not recommended for first-line treatment of CP, with the exception of extremely severe and acute cases of inflammatory dermatoses and as a short-term treatment in selected cases of refractory CP, especially in paraneoplastic pruritus and palliative care.
- UV phototherapy is recommended for refractory CP in inflammatory skin diseases, cutaneous lymphoma, CPG and selected cases of systemic pruritus (e.g. CKD-associated pruritus, cholestatic pruritus, aquagenic pruritus), especially in elderly pruritus patients or in case of contraindications for systemic therapy. We suggest UV phototherapy in combination with topical and/or systemic treatment, with the exception of calcineurin inhibitors and immunosuppressant drugs.
- Gabapentinoids (gabapentin, pregabalin) are recommended in neuropathic CP and in CKD-associated pruritus and suggested for the treatment of refractory CP and PUO.
- We suggest μ-opioid receptor antagonists in refractory CP, especially in cholestatic pruritus.
- Selected antidepressants are recommended for psychogenic CP and for refractory CP, especially in malignant, cholestatic and chronic kidney disease.

- Neurokinin receptor 1 antagonists like e.g. serlopitant can be recommended in refractory CP and CPG.
- Serotonin receptor antagonists are not recommended for the treatment of CP and CPG.

Table 1. Systemic diseases that can induce pruritus (examples)

Metabolic and endocrine diseases	o Chronic kidney disease (CKD) o Hepatobiliary diseases with or without cholestasis o Hyperparathyroidism o Hyper- and hypothyroidism o Iron deficiency o Diabetes mellitus
Infective diseases	o HIV and AIDS o Parasitoses including helminthosis o Viral hepatitis
Haematological disorders	o Polycythemia vera, myeloproliferative diseases o Lymphoma, e.g. Hodgkin lymphoma
Neurological diseases	o Multiple sclerosis o Brain tumours o Notalgia paraesthetica o Brachioradial pruritus o Postherpetic neuralgia o Small-fibre neuropathies
Psychiatric or psychosomatic diseases	o Depression o Anxiety o Delusional disorders o Eating disorders

Table 2. Drugs that may induce or maintain chronic pruritus (without a rash)

Class of drug	Substance (examples)
ACE inhibitors	Captopril, enalapril, lisinopril
Anti-arrhythmic agents	Amiodarone, disopyramide, flecainide
Antibiotics	Amoxicillin, ampicillin, cefotaxime, ceftriaxone, chloramphenicol, ciprofloxacin, clarithromycin, clindamycin, cotrimoxazole, erythromycin, gentamycin, metronidazole, minocycline, ofloxacin, penicillin, tetracycline
Antidepressants	Amitryptyline, 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
Angiotensin II antagonists	Irbesartan, telmisartan, valsartan
Betablockers	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
Immunosuppressive drugs	Cyclophosphamide, cyclosporin, methotrexate, mycophenolatmofetil, tacrolimus, thalidomide
Antilipids	Clofibrate, fenofibrate, fluvastatin, lovastatin, pravastatin, simvastatin
Neuroleptics	For instance, chlorpromazine, haloperidol, risperidone
Plasmaexpanders, blood supplying drugs	Hydroxyethyl starch, pentoxifylline
Tranquilizers	Alprazolam, chlordiazepoxidd, lorazepam, oxazepam, prazepam
Uricostatics	Allopurinol, colchicine, probenecid, tiopronin

Table 3. Diagnostics: laboratory screening, diverse approaches and investigations

Chronic pruritus: first-step lab screening	• Differential blood cell count, erythrocyte sedimentation rate (ESR) • Creatinine, urea • Transaminases (ASAT,ALAT), alkaline phosphatase, gamma-glutamyltransferase (y-GT) • Lactate dehydrogenase (LDH) • TSH • Glucose • Ferritin, C-reactive protein (CRP) • Age > 40 y: stool occult blood
Chronic pruritus: further investigations	• Immunoelectrophoresis • Hepatitis serology, cholesterol, triglycerides • Calcium, parathormone • Biopsy with DIF (mastocytosis, pemphigoid, etc.) • Swab for candida (mucocutaneous pruritus) • Urine: mast cell metabolites • Further imaging studies and bone marrow investigation for mastocytosis
Chronic pruritus: approach I	• Detailed history: preceding skin changes? • Weight loss, fever, night sweats, fatigue? • Emotional stress? • Medication? Drug abuse? • Physical examination • Subtle primary skin disorders: xerosis, scabies • Bath oil, emollient/education • Follow-up appointment after 2 weeks
Chronic pruritus: approach II	• Detailed history renewed • Lab screening (see above) • Detailed general physical examination: LN, rectal • Stool for parasites • Chest X-ray • Biopsy • Complete internist work-up, further imaging • Follow-up

Table 4. Laboratory and technical investigations in chronic pruritus (CP) due to systemic diseases

Laboratory and technical screening-basic	Complete blood count, creatinine, urea, ASAT, ALAT, alkaline phosphatase, y-GT, TSH, TSH, glucose, chest X-ray, (stool test for parasites in genito-anal pruritus)
Metabolic and endocrine diseases	
Renal insufficiency	Lab I: Creatinine (and urea for elderly) Lab II: Calcium, phosphate, parathormone, HCO3, urinalysis with urine protein concentration. ANA, anti-ds-DNA-Ab, ANCAs, anti-GBM-Ab, etc. Tech: Sonography of the kidneys, CT or MRI
Liver diseases with or without cholestasis	Lab I: ALAT, ASAT, y-GT, alkaline phosphatase, HBV-, HCV-serology Lab II: Bilirubin, LDH, antimitochondrial antibodies (AMA), anti-smooth muscle Ab (SMA), antiactin Ab, ANA, ANCA 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 II: Only serum-calcium is elevated Calcium, parathormone phosphate, vitamin D (1,25-Vit D, 25-Vit D) Tech: sonography of the parathyroid glands, scintigraphy, MRI
Hyper- and hypothyroidism	Lab I: TSH Lab II: fT3, fT4, thyroid peroxidase antibody; thyroglobulin antibody; thyroid stimulating hormone receptor antibody.Tech: Sonography of thyroid gland
Anaemia	Lab I: Complete blood count including MCV and MCHC, LDH, ferritin Lab II: Reticulocytes, haptoglobin, vitamin B12, folic acid. Lab II: Bone marrow aspiration
Iron deficiency	Lab I: Ferritin Lab II: Serum iron, transferrin, transferrin saturation (TSAT). stool occult blood.
Malabsorption	Lab tests only in case of typical history (known pancreatic disease, history of intestinal surgery) or symptoms such as chronic diarrhoea or steatorrhoea and weight loss. Lab II: Serum protein and serum albumin, gliadin antibody Vitamin A (hyperkeratosis due to vitamin A deficiency), vitamin B12 (neuropathy due to vitamin B deficiency) Tech: endoscopy with biopsy

Other diseases	
Pruritus of the elderly	Lab I: Differential blood count, creatinine, urea, estimated glomerular filtration rate (eGFR), ALAT, ASAT, alkaline phosphatase, TSH
Infectious diseases	In the case of clinical suspicion due to history: HIV antibodies, In the case of clinical suspicion due to history and/or when eosinophilia was found in differentiated blood count: Stool culture and microscopic examination for parasites
Haematological disorders	**Polycythemia vera** Lab I: Blood count (elevated haematocrit and haemoglobin, increase of red blood cells, leukocytosis, thrombocytosis), ESR Lab II: To rule out secondary erythrocytosis: erythropoietin (EPO), JAK2 V617F Lab III: Bone marrow Tech: Abdominal sonography, CT or MRI **Lymphoma** Lab I: Blood count, ESR Lab II: Bone marrow, flow cytometry Tech: Sonography, thoracoabdominal CT or MRI
Neurological diseases	In the case of suspected neurological disorder: Lumbar puncture and MRI **Multiple sclerosis** Lab : Cerebrospinal fluid analysis (oligoclonal bands?) Tech: MRI (CT) of brain **Brain tumours** Lab: Cerebrospinal fluid analysis with histopathology Tech: MRI (CT) of brain **Notalgia paraesthetica** MRI of thoracic spine **Brachioradial pruritus** MRI of thoracic and cervical spine
Psychiatric or psychosomatic diseases	Psychiatric assessment, with short questionnaire for depressive and anxiety disorders
Pregnancy with or without cholestasis	Lab I: ASAT, ALAT, AP, y-GT Lab II: Bile acids, bilirubin, serology for HAV, HBV, HCV, EBV and CMV, 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 the case of HES exposure (electron microscopy)

Fig. 1. Diagnostic algorithm

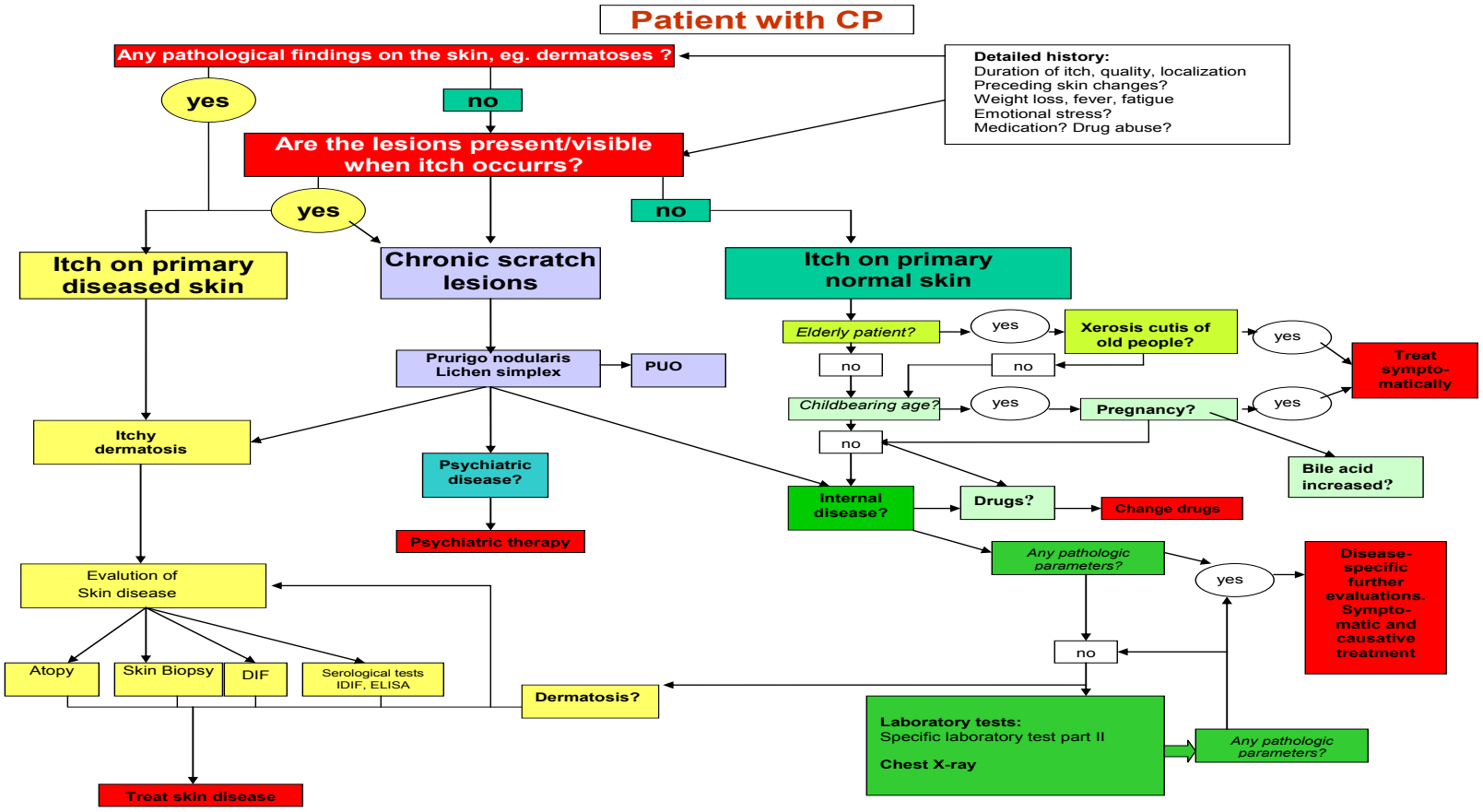

Table 5. General measures for treating chronic pruritus (CP)

Application of:	Soft clothing permeable to air, e.g. cotton. Dress in layers to avoid sweating Low room temperature at night
	Mild, non-alkaline, perfume-free soaps, moisturizing syndets and shower/bath oils
	Skin moisturizer on a daily basis, especially after showering and bathing. Emollients, especia creams/lotions/gels with, e.g. urea (5%–10%), glycerol (20%), camphor (2%), menthol (1%), pramoxine (1%), polidocanol (2%–10%)
	Luke-warm water, bath (max 20 min), possibly adding oatmeal or potassium permanganate skin dry after bathing
	Cooling wet or fat-moist wraps
Avoidance of	Factors that can contribute to dry skin, such as dry climate, sauna, alcoholic compresses, frequent washing and bathing
	Excitement, strain, negative stress
	Very hot and spicy foods, large amounts of hot drinks and alcohol
	Contact with allergenic and irritant substances (e.g. fragrances, preservatives and surfactant
Relaxation techniques	Autogenic training, relaxation therapy, psychosocial education
Education	Educational training programs for coping with the vicious itch-scratch-itch cycle (Staab, D 2006, Weisshaar, Diepgen et al. 2008, Bathe, Matterne et al. 2009)

Table 6. Therapeutic options in CKD-associated pruritus

Therapeutic options in renal pruritus	
Antipruritic effects in controlled studies	- Activated charcoal 6g/day (Bernhard 1994) - Gabapentin 300 mg 3x/week postdialysis (Gunal, Ozalp et al. 2004), pregabalin 50 mg/every other day (Foroutan, Etminan et al. 2017) - Gamma-linolenic acid cream 3x/day (Chen, Chiu et al. 2006) - Capsaicin 3-5x/day (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/day (Silva, Viana et al. 1994) - Montelukast 10 mg/day (Mahmudpour, Roozbeh et al. 2017)
Equivocal effects in controlled studies	- Naltrexone 50 mg/day (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 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 body weight 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 7. Therapeutic options in hepatic and cholestatic pruritus

Therapeutic options in hepatic and cholestatic pruritus	
Antipruritic effects in controlled studies	• Cholestyramine 4-16 g/day (not in primarily biliary cirrhosis!) (Bergasa, Mehlman et al. 2000) • Ursodesoxycholic acid 13-15 mg/kg/day (Goulis, Leandro et al. 1999, Kong, Kong et al. 2016) • Rifampicin 300-600 mg/day (Ghent and Carruthers 1988); Kremer, van Dijk 2012) • 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/day (Bergasa, Alling et al. 1999) • Sertraline75-100 mg/day (Mayo, Handem et al. 2007) • Thalidomide 100 mg/day (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, O'Donohue, Haigh et al. 1997, Muller, Pongratz et al. 1998) • In PBC: bezafibrate 400 mg/day in combination with ursodesoxycholic acid (Yin, Li et al. 2015, Corpechot, Chazouillères et al. 2018)
Antipruritic effects in case reports	• PBC: Nalfurafine (Yagi, Tanaka et al. 2018) • Phenobarbital 2-5 mg/kg KG/day (Raiford 1995) • Stanozolol 5 mg/day (Walt, Daneshmend et al. 1988) • Paroxetine (Kraut 2017) • Phototherapy: UVA, UVB(Fleischer 2000) • Bright light therapy (10.000 Lux) reflected toward the eyes up to 60 min twice/day (Bergasa, Link et al. 2001) • Etanercept 25 mg sc. 2x/week (Epstein and Kaplan 2004) • Nasobiliary drainage (Appleby, Hutchinson et al. 2015) • 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 8. Antipruritic therapy of atopic dermatitis (AD)

Antipruritic therapy of atopic dermatitis (Wollenberg, Oranje et al. 2016) and Weollenberg 2018, part I and part II	
Antipruritic effects confirmed in controlled studies:	• Glucocorticosteroids (topical and oral) • Cyclosporin A • Mycophenolate mofetil (MMF 2 g/day or EC-MPS 1440 mg/day) * • Dupilimab (Simpson, Bieber et al. 2016) (300 mg /weekly or /2 weeks) • Tacrolimus ointment (2x/d) • Pimecrolimus cream (2x/d) • Proactive therapy with steroids and tacrolimus ointments (2x/week) • Naltrexone 50 mg/d (Brune, Metze et al. 2004, Malekzad, Arbabi et al. 2009)
Equivocal results:	• Antihistamines (topical and systemic) • Allergen-specific immunotherapy (ASIT) • Azathioprine (2–5 mg/kg/day, starting dose 50 mg/day) • Methotrexate (5–25 mg 1x/week) • Apremilast (20–30 mg 2x/day; dosage from BNF) • Interferon gamma, i.c.
Antipruritic effects shown in case reports:	• Intravenous immunoglobulins (IVIG) • UVA1-/UVB 311 nm / PUVA therapy • Leukotriene antagonists (e.g. zafirlukast/montelukast) • Capsaicin (3-5x/d) • Immunoabsorption • Anti-TNFα therapy (infliximab 10 mg/kg for 7 cycles) • Omalizumab (150 mg for 10 cycles) • Combination omalizumab with IVIG or rituximab

Table 9. Therapeutic options in polycythaemia vera

Therapeutic options in polycythaemia vera	
Effects shown in case reports	• Paroxetine 20mg/d (Diehn and Tefferi 2001, Tefferi and Fonseca 2002) • Hydroxyzine (Diehn and Tefferi 2001) • Fluoxetine 10mg/d(Tefferi and Fonseca 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 10: Therapeutic options in Aquagenic Pruritus

Effects confirmed in case reports (Steinman and Greaves 1985, Wolf and Krakowski 1988, Shelley and Shelley 1998) *Effects confirmed in RCT*	• 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, UVA + NB-UVB (Menage, Norris et al. 1993, Jahn, von Kobyletzki et al. 1997, Martinez-Escribano, Quecedo et al. 1997, Xifra, Carrascosa et al. 2005, Koh and Chong 2009) • Propranolol 10 to 80 mg/d (Nosbaum, Pecquet et al. 2011) • Atenolol 25mg/d (Cao, Yong et al. 2015) • Clonidine 0.1 mg twice/d • Astemizol 10 mg/d • Ibuprofen (prior to bathing) • Pregabalin 150-300 mg/day • Antihistamines, e. g. hydroxizine 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 (Phan, Bernhard et al. 2010) • 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 • Acetylic salicylic acid 300–500 mg/day

Table 11. Stepwise symptomatic-therapeutic approach in chronic pruritus (> 6 weeks)

	Therapy
Step 1	• General therapeutic measures **(Table 5)**, especially basic therapy with moisturisers • Initial symptomatic therapy: systemic H1 antihistaminics*, topical corticosteroids
Step 2	• Symptomatic causative-adapted therapy **(Tables 6–10)** if origin is unknown
Step 3	• In pruritus of unknown origin or therapy refractory cases in step 2: symptomatic topical therapy, especially in localised forms with, e. g. calcineurin inhibitors, cannabinoid agonists, capsaicin and/or systemic therapy with gabapentin or pregabalin, antidepressants (doxepin, mirtazapine, paroxetine), UV phototherapy, naltrexone, immunosuppressants (cyclosporine)
Concomitant treatment in every step	• Diagnostics and treatment of underlying disease • General therapeutic measures **(Table 5)** • **In sleep disorders: sedative H1-antihistaminics, tranquilisers, tricyclic antidepressants or neuroleptics** • Psychosomatic care, behavioural therapy for scratch behaviour • In erosive scratch lesions: topical antiseptics, topical corticosteroids

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

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t. E. D. F. (EDF), t. E. A. o. D. a. V. (EADV), t. E. A. o. A. a. C. I. (EAACI), t. E. T. F. o. A. D. (ETFAD), E. F. o. A. a. A. D. P. A. (EFA), t. E. S. f. D. a. P. (ESDaP), t. E. S. o. P. D. (ESPD), G. A. a. A. E. N. (GA2LEN) and t. E. U. o. M. S. (UEMS) (2018). " Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I." J Eur Acad Dermatol Venereol 32(5): 657-682.
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Conflicts of interests

The Work Under Consideration for Publication					
		Weißhaar, Elke	**Garcovich, Simone**	**Ständer, Sonja**	**Streit, Markus**
1	Grant	None	None	None	None
2	Consulting fee or honorarium	None	None	None	None
3	Support for travel to meetings for the study or other purposes	None	None	None	None
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	None	None	None	None
5	Payment for writing or reviewing the manuscript	None	None	None	None
6	Provision of writing assistance, medicines, equipment, or administrative support	None	None	None	None
7	Other	None	None	None	None

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Relevant financial activities outside the submitted work					
1	Board membership	Galderma, Menlo	Celgene, Menlo Therapeutics, Abbvie, Pierre Fabre	Beiersdorf, Celgene, Galderma, Kiniksa, Menlo, NeRRe, Novartis, Sienna, Trevi	yes
2	Consultancy	None	None	Beiersdorf, Celgene, Galderma, Kiniksa, Menlo, NeRRe, Novartis, Sienna, Trevi	None
3	Employment	None	None	None	None
4	Expert testimony	None	None	None	None
5	Grants/grants pending	None	None	None	None
6	Payment for lectures including service on speakers bureaus	Münster Pruritus workshop 6.-	None	None	yes

		8.9.2018			
7	Payment for manuscript preparation	None	None	None	None
8	Patents (planned, pending or issued)	None	None	None	None
9	Royalties	None	None	None	None
10	Payment for development of educational presentations	None	None	None	None
11	Stock/stock options	None	None	None	None
12	Travel/accommodations/meeting expenses unrelated to activities listed**	None	None	None	None
13	Other (err on the side of full disclosure)	Principal Investigator for Menlo and TREVI	None	Investigator for Dermasence, no honorarium	None

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The Work Under Consideration for Publication					
		Gieler, Uwe	**Misery, Laurent**	**Şavk, Ekin**	**Mettang, Thomas**
1	Grant	None	None	None	None
2	Consulting fee or honorarium	None	None	None	None
3	Support for travel to meetings for the study or other purposes	None	None	None	None
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	None	None	None	None
5	Payment for writing or reviewing the manuscript	None	None	None	None
6	Provision of writing assistance, medicines, equipment, or administrative support	None	None	None	None
7	Other	None	None	None	None

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Relevant financial activities outside the submitted work					
1	Board membership	Galderma (Rosacea) Lilly (Psoriasis) AbbBie (Psoriasis/Hidradenitis supp) Almirall (Adherence)	Bayer Lilly Menlo Novartis Pierre Fabre Sanofi Trevi	None	None
2	Consultancy	None	Amgen Bayer Beiersdorf Celgene Expanscience Lilly Nestlé Pierre Fabre	None	None
3	Employment	Univ. Dept Dermatology University Giessen / Dept. of Dermatology / Hamad Medical Cooperation Doha Qatar	None	None	None
4	Expert testimony	None	None	None	None
5	Grants/grants pending	PsoTrain/grant (AbbVie)	BASF Beiersdrof Celgene	None	None

			Clarins Expanscience Johnson&Johnson Pierre Fabre Uriage		
6	Payment for lectures including service on speakers bureaus	Galderma AbbVie Almirall Bayer Beiersdorf Galderma GSK Janssen Johnson&Johnson Leo Lilly Merz Novartis Pierre Fabre Roche Posay Sanofi Vichy	Abbvie Bioderma Celgene Janssen Leo Novartis Pfizer Pierre Fabre Roche-Posay Sanofi UCB	None	FMC – speakers honorary for Peritoneal dialysis
7	Payment for manuscript preparation	Almirall (Adherence Paper Am J Clin Dermatol) Galderma (Burden of Rosacea, submitted)	Beiersdorf Bioderma Pierre Fabre Sanofi	None	None
8	Patents (planned, pending or issued)	None	None	None	None
9	Royalties	None	None	None	None
10	Payment for development of educational presentations	Atopic dermatitis academy Hessen payed by insurance companies	Abbvie Celgene Intercept	None	None
11	Stock/stock options	None	None	None	None
12	Travel/accommodations/meeting expenses unrelated to activities listed**		Abbvie Janssen Lilly Novartis Pfizer Sanofi	None	None
13	Other (err on the side of full disclosure)		Amgen Biogen Galderma GSK Janssen Leo Lilly Novartis Sanofi Trevi	None	None

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The Work Under Consideration for Publication					
		Wallengren, Joanna	**Dalgard, Florence**	**Gimenez Arnau**	**Szepietowski, Jacek C.**
1	Grant	None	None	BAYER Pruritus management in Contact Dermatitis	None
2	Consulting fee or honorarium	None	None	None	None
3	Support for travel to meetings for the study or other purposes	None	None	None	None
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	None	None	None	None
5	Payment for writing or reviewing the manuscript	None	None	None	None
6	Provision of writing assistance, medicines, equipment, or administrative support	None	None	None	None
7	Other	None	None	None	None

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Relevant financial activities outside the submitted work					
1	Board membership	None	None	URIACH, NOVARTIS, GENENTECH, SANOFI	AbbVie, Celgene, Galenica, Leo Pharma, Pierre-Fabre, Novartis, Menlo, Trevi
2	Consultancy	None	None	None	Dignity Sciences, Sanzoz
3	Employment	None	None	None	No
4	Expert testimony	None	None	None	No
5	Grants/grants pending	None	None	URIACH, NOVARTIS, Instituto Carlos III-FEDER	No
6	Payment for lectures including service on speakers bureaus	None	None	URIACH, NOVARTIS, MENARININ, LEO-PHARMA	AbbVie, Galenica Janssen, Leo Pharma, Novartis, SunFarm, Sandoz, Eli Lilly
7	Payment for manuscript preparation	None	None	None	Galenica
8	Patents (planned,	None	None	None	None

	pending or issued)				
9	Royalties	None	None	None	None
10	Payment for development of educational presentations	None	None	URIACH, NOVARTIS, MENARININ	None
11	Stock/stock options	None	None	None	None
12	Travel/accommodations/meeting expenses unrelated to activities listed**	None	None	None	Medac
13	Other (err on the side of full disclosure)	None	None	None	None

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Other relationships					
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The Work Under Consideration for Publication					
		Lambert, Julien	**Leslie, Tabi**	**Tschachler, Erwin**	**Name**
1	Grant	None	None	Channel SA	
2	Consulting fee or honorarium	None	None	None	
3	Support for travel to meetings for the study or other purposes	None	None	None	
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	None	None	None	
5	Payment for writing or reviewing the manuscript	None	None	None	
6	Provision of writing assistance, medicines, equipment, or administrative support	None	None	None	
7	Other	None	None	None	

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Relevant financial activities outside the submitted work					
1	Board membership	Novartis, Leo Pharma, Celgene	None	None	
2	Consultancy	Novartis, Leo Pharma, Celgene	None	None	
3	Employment	None	None	None	
4	Expert testimony	None	None	None	
5	Grants/grants pending	None	None	None	
6	Payment for lectures including service on speakers bureaus	Novartis, Leo Pharma, Celgene	None	None	
7	Payment for manuscript preparation	None	None	None	
8	Patents (planned, pending or issued)	None	None	None	
9	Royalties	None	None	None	
10	Payment for development of educational presentations	None	None	None	
11	Stock/stock options	None	None	None	
12	Travel/accommodations/meeting expenses unrelated	Novartis, Celgene	None	None	

	to activities listed**				
13	Other (err on the side of full disclosure)	None	None	None	

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Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	None	Unpaid advisory: Novartis Menlo	None	