ORIGINAL REPORT

European S2k Guideline on Chronic Pruritus

In cooperation with the European Dermatology Forum (EDF)

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ABSTRACT

Pruritus is a frequent symptom in medicine. Population-based studies show that one in five persons in the general population has suffered from chronic pruritus (CP) at least once in their lifetime, with a 12-month incidence of 7%. CP, which can affect all age groups, is associated with numerous, often interdisciplinary medical conditions. It needs a precise diagnostic work-up to identify causes and relevant comorbidities. Management of CP comprises treatment of the underlying disease as well as topical and systemic therapies. Treating CP needs to be targeted, multimodal and performed in a step-wise procedure requiring an interdisciplinary approach. In recent years, novel in-label therapies have been approved for CP, including therapies for chronic prurigo, uraemic and cholestatic pruritus. We present the updated European guideline on chronic pruritus by a team of European experts from different disciplines.

This version is an updated version of the guideline that was published in 2019 (www.euroderm.org).

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Conflict of Interest**: see table enclosed**

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Abbreviations and explanations	
AAA	Anti-actin antibodies
ACE	Angiotensin-converting enzyme
AD	Atopic dermatitis
AEP	Atopic eruption of pregnancy
AIDS	Acquired immunodeficiency syndrome
ALAT	Alanine amino transferase
AMA	Anti-mitochondrial antibodies
ANA	Anti-nuclear antibody
ANCA	Anti-neutrophil cytoplasmic antibody
Anti-ds-DNA-Ab	Anti-double-stranded DNA antibody
Anti-GBM-Ab	Anti-glomerular basement membrane antibody
AP	Alkaline phosphatase
ASAT	Aspartate amino transferase
ASMA	Anti-smooth muscle antibody
AST	Aspartate transaminase
ATX	Autotaxin
BB	Broadband
CaP	Calcium phosphate
CGRP	Calcitonin gene-related peptide
CKD	Chronic kidney disease
CKD-aP	Chronic kidney disease-associated pruritus
CMV	Cytomegalovirus
CNS	Central nervous system
CP	Chronic pruritus
CPG	Chronic prurigo
CRP	C-reactive protein
CSU	Chronic spontaneous urticaria
CT	Computed tomography
DIF	Direct immunofluorescence
DM	Dermatomyositis
EBV	Epstein–Barr virus
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EPO	Erythropoietin
ERC	Endoscopic retrograde cholangiogram
ESR	Erythrocyte sedimentation rate
FT3	Free triiodothyronine
FT4	Free thyroxine
GABA	ɣ-Aminobutyric acid
GAD-7	Generalized Anxiety Disorder-7 questionnaire
ɣ-GT	ɣ-Glutamyltransferase
GPQ	German Pruritus Questionnaire
HADS	Hospital Anxiety and Depression Scale
HAV	Hepatitis A virus
HbA1c	Haemoglobin A1c
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HES	Hydroxyethyl starch
HIV	Human immunodeficiency virus
HRQOL	Health-related quality of life
ICP	Intrahepatic cholestasis of pregnancy
IDIF	Indirect immunofluorescence
IENFD	Intra-epidermal nerve fibre density
IFSI	International Forum on the Study of Itch
IgE	Immunoglobulin E
IIF	Indirect immunofluorescence
IL	Interleukin
ISS	Itch Severity Scale
Itch	Synonym of pruritus
ItchyQOL	Itch-related quality of life measure
JAK	Janus kinase
LDH	Lactate dehydrogenase
LPA	Lysophosphatidic acid
LPC	Lysophosphatidylcholine
MARS	Molecular adsorbent recirculation system
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MRC	Magnetic resonance cholangiogram
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NB	Narrowband
NRS	Numerical rating scale
NSAID	Non-steroidal anti-inflammatory drug
PAR	Proteinase-activated receptor
PASI	Psoriasis area and severity index
PBC	Primary biliary cholangitis
PCR	Polymerase chain reaction
PEP	Polymorphic eruption of pregnancy
PG	Pemphigoid gestationis
PHQ-8	Eight-item version of the Patient Health Questionnaire
PN	Prurigo nodularis
PPE	Pruritic papular eruption
PTH	Parathyroid hormone
PUO	Pruritus of undetermined origin
PUVA	Psoralen and ultraviolet A
PV	Polycythaemia vera
PXR	Pregnane X receptor
RCT	Randomised controlled trials
SSD	Somatic symptom disorder
SSRI	Selective serotonin reuptake inhibitors
SSS	Somatic symptom scale
TCI	Topical calcineurin inhibitor
TRP	Transient receptor potential
TSAT	Transferrin saturation
TSH	Thyroid-stimulating hormone
UAS7	Urticaria activity score
UP	Uraemic pruritus
UV	Ultraviolet
UVA	Ultraviolet A
UVB	Ultraviolet Bf
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 can occur in many skin and systemic diseases (Weisshaar and Dalgard 2009). Due to its severity and chronicity as well as the fact that it is frequently refractory to therapy, it causes a high burden (Stewart 2010, Dalgard, Svensson et al. 2020), impairs quality of life of the affected individuals (Rodriguez, Kwatra et al. 2023) and burdens the health care system (Pereira, Farcas et al. 2021, Ständer, Ketz et al. 2024).

This guideline addresses all affected patient groups (regarding age, sex and ethnicity) causes and phenotypes of CP (Sinikumpu, Jokelainen et al. 2023). In its early stage, CP is considered a symptom of the underlying disease. However, with time, CP may develop its own dynamics that is no longer linked to the course of the underlying disease. In this stage, and much like chronic pain, CP can be considered a distinct symptom 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 patient management including a diagnostic and therapeutic approach that is applicable to all types of CP. The management of CP often needs to be multidisciplinary. However, as a consequence of the diversity of possible underlying diseases, CP should be addressed individually in each patient. Studies have demonstrated that early intervention in certain types of CP may lead to a significant improvement (e.g. therapy of polycythaemia vera (PV)-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 frequency, diversity and complexity of CP as well as by the limitation of well-defined outcome measures, biomarkers and therapy targets. To complicate matters, RCTs do exist, but only for some types of pruritus, and the results are sometimes conflicting. 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), chronic prurigo [CPG] (Ständer, Pereira et al. 2020), urticaria (Zuberbier, Aberer et al. 2018), scabies (Salavastru, Chosidow et al. 2017), adult palliative care (Siemens, Xander et al. 2016, Ständer, Pereira et al. 2020)). The increasing complexity of CP, coupled with ever-growing health care costs and diminished economic health care resources, increases 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 mostly topical and systemic therapies can only be prescribed "off-label" and might 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 authors of this guideline agreed to use this terminology. All accepted pruritus and itch to be synonyms. The first definition of pruritus by Samuel Hafenreffer ("*Pruritus is an unpleasant sensation that provokes the desire to scratch*") (Savin 1998) dates back to 1660 and was used until very recently. In 2024, a new definition was established by the international, interdisciplinary, interprofessional IDEOM (International Dermatology Outcome Measure) Itch Workgroup:

Definition of pruritus as a sensation: "Pruritus (itch) is an unpleasant sensation of the skin and/or neighbouring mucous membranes* commonly triggering an urge to scratch. Pruritus can be triggered, worsened or improved by a broad variety of external and internal factors".

Definition of pruritus as a disease: CP is defined by its intermittent or continuous course over at least 6 weeks. CP can vary substantially in duration, intensity, quality, course, extent, location and impact on personal, social or professional quality of life (QOL) and health. CP typically differs from acute pruritus by long-term structural and functional changes of itch processing (Ständer, Augustin et al. 2013, Ständer, Schmelz et al., 2025).

Pruritus may be a symptom of diseases. It can persist independently despite the resolution of the original disease or trigger and become a disease in its own right (CP) (Ständer, Pogatzki-Zahn et al. 2015).

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's 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 classifies the broad and heterogeneous spectrum of CP patients into three groups based on their skin condition: Patients with pruritus on primarily diseased/inflamed skin are classified into "Group I", patients with primarily normal skin into "Group II" and patients with characteristic, chronic secondary scratch lesions into "Group III" (Ständer, Weisshaar et al. 2007). The last group also includes CPG, a disease defined by CP, prolonged scratching behaviour and the development of localised or generalised hyperkeratotic pruriginous lesions (i.e. including nodules [prurigo nodularis, PN], papules and plaques (Pereira, Steinke et al. 2018)). In this context, it is important to differentiate the adjective "pruriginous" versus "pruritic": "Pruriginous" refers to the phenotypic lesions observed in PN, "pruritic" to the symptom of skin lesions associated with pruritus.

According to this classification, the aetiology of CP is classified into categories such as "dermatological" (including pregnancy-related dermatoses), "systemic" (including drug-induced pruritus), "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, Steinhoff, Schmelz et al. 2018, Steinhoff, Oaklander et al. 2019). In most cases, this is better described as neuropathic pruritus inducing an overlap of pain, pruritus and par- or dysaesthetic sensations (also referred to as "pruralgia"). Somatoform pruritus is defined as pruritus in which 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 are increasing. The Global Burden of Disease study listed pruritus as one of the 50 most common symptoms leading to high burden (Hay, Johns et al. 2014). 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). A recent study in Germany estimated that the prevalence of prurigo was 0.21% and 2.21% for pruritus, while the incidence of new cases was 0.13% for CPG and 1.51% for pruritus (Augustin, Garbe et al. 2021).

In a recent population-based Polish study, it was estimated that for the period 2016–2018, the prevalence of PN increased from 5.82 to 6.52 cases per 100,000 population (Ryczek and Reich 2020). 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).

Only few studies have addressed the frequency of pruritus in primary care. In an Australian study, 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) resembling a 1% sample of England and Wales showed pruritus and related conditions to be present in 1.04% of consultations (male, 0.73%; female, 1.33%). In a study conducted in Crete, Greece, pruritus was diagnosed in 6.3% of 3715 primary care 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 (Frese, Herrmann et al. 2011). The prevalence of itch in the elderly was estimated to be between 11.5% and 41.0% (Cao, Tey et al. 2018, Reszke, Białynicki-Birula et al. 2019). The reader is referred to Sect. 4.2 for a

more detailed discussion of the epidemiology of CP in specific patient populations.

4. THE SPECTRUM OF CHRONIC PRURITUS

The classification of CP has two aspects (see Sect. 2): the clinical phenotype and the underlying aetiology. Regarding the former, pruritus can occur in conjunction with dermatoses or on normal-appearing, non-lesional skin with/without scratch lesions. Once the aetiology has been determined, a categorisation of the pruritus type can be made. Determination of the aetiology is essential in order to drive treatment. The phenotype may help in finding the aetiology and determining treatment according to dermatological principles.

4.1. Pruritus-associated skin lesions

CP may occur as a symptom of dermatoses, accordingly along with primary skin lesions (IFSI Group I), as well as systemic, neurologic and psychiatric/psychosomatic diseases or due to drugs without the presence of primary skin lesions (IFSI Group II) (Ständer, Weisshaar et al. 2007). In IFSI group II, the skin may appear normal or have skin lesions induced by scratching. 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 is unable to alleviate itch (e.g. cholestatic pruritus); in other diseases, scratching even leads to a worsening of itch (e.g. symptomatic dermographism). In both conditions, scratching is accordingly avoided. These differences hinder scratching behaviour or scratch lesions from serving as common objective markers for the severity of itch. Patients can develop CPG, which may present as chronic nodular prurigo or other subtypes (Pereira, Steinke et al. 2018). In these cases, an underlying aetiology or in some cases also clinical diagnosis can be difficult to establish and diagnostics should be performed (Ständer, Pereira et al. 2020).

4.2. Categorisation of CP according to underlying condition(s)

Systemic diseases frequently accompanied by pruritus are summarised in **Table 1**. In recent years, several subtypes of CP on lesional and non-lesional skin have been characterised in more detail. Some of the most frequent systemic diseases inducing CP and predominantly affecting patient populations are presented in the following sections.

4.2.1. Pruritus in chronic kidney disease

CKD-associated pruritus (CKD-aP), previously also referred to as uraemic pruritus (UP), is comparatively frequent and difficult to treat. According to the Dialysis Outcomes and Practice Patterns Study (DOPPS) data comprising information from many different countries, moderate to severe CKD-aP is reported to affect up to 30% of patients on dialysis (Rayner, Larkina et al. 2017). Likewise, a representative study (German Epidemiological Hemodialysis Itch Study, GEHIS) found that around one third of patients on haemodialysis (HD) complained of CP. In 177 HD patients, 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). Follow-up data showed that the cumulative 3-year incidence of CKD-aP is about 17% (Ofenloch, Grochulska et al. 2022, Ofenloch, Grochulska et al. in press).

The pathophysiology of CKD-aP 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 systemic micro-inflammation, which is relatively frequent in uraemia (Mettang, Pauli-Magnus et al. 2002, Kimmel, Alscher et al. 2006). Two uraemic toxins, p-cresylsulfate and indoxylsulfate, were recently suggested to be involved in the pathogenesis of CP in kidney disease, probably by induction of protease-activated receptor-2 (PAR-2) expression in keratinocytes (Wang, Lu et al. 2016). Recently, the hypothesis that calcium phosphate (CaP) deposition in the skin may be

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

Metabolic and endocrine diseases	• Chronic kidney disease
	• Hepatobiliary diseases with or without cholestasis
	• Hyperparathyroidism
	• Hyper- and hypothyroidism
	• Iron deficiency
	• Diabetes mellitus
Infectious diseases	• HIV and AIDS
	• Parasitoses including helminthosis
	• Viral hepatitis
Haematological disorders	• Polycythaemia vera, myeloproliferative diseases
	• Lymphoma, e.g. Hodgkin's lymphoma
Neurological diseases	• Multiple sclerosis
	• Neuromyelitis optica
	• Brain tumours
	• Notalgia paraesthetica
	• Brachioradial pruritus
	• Post-herpetic neuralgia
	• Small-fibre neuropathies
Psychiatric or psychosomatic diseases	• Depression
	• Anxiety
	• Delusional disorders
	• Eating disorders

involved in CKD-related itch has been focused on in more detail (Keshari, Sipayung et al. 2019). In recent years, the role of cytokines in the pathogenesis of CKD-aP has been focused in particular on interleukin (IL)-31, which seems to be of importance as a mediator of itch in skin diseases (Cevikbas and Lerner 2020). Another concept proposes that an imbalance, e.g. through accumulation of endogenous opioids binding either μ- (MOR) or κ- (KOR) opioid receptors might contribute to the induction of CKD-aP (Umeuchi, Togashi et al. 2003). Skin biopsies of haemodialysis patients with CKD-aP showed significantly lower KOR expression than the skin of non-pruritic patients with, at the same time, comparable MOR expression in both groups. Additionally, KOR expression correlated negatively with the intensity of CKD-aP (Wieczorek, Krajewski et al. 2020). Allantoin has recently been suggested to play an important role in CKD-aP, mediated by Mas-related G-protein coupled receptor member D (MRGPRD) and transient receptor potential vanilloid type 1 (TRPV1), in CKD patients (Yang, Sun et al. 2023).

4.2.2. 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, Düll and Kremer 2019, Hirschfield, Shiffman et al. 2023, Hirschfield, Bowlus et al. 2024, Kremer, Mayo et al. 2024). It is often termed "cholestatic" pruritus, although cholestasis or jaundice are not a prerequisite of pruritus related to hepatobiliary diseases. Cholestatic pruritus 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 at 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 (ICP) and paediatric cholestatic disorders (Beuers, Kremer et al. 2014, Kremer, Bolier et al. 2014, Kremer, Namer et al. 2015), with the exception of PBC (Fujino, Tanaka et al. 2019), 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 MOR antagonists such as nalmefene and naltrexone supports the hypothesis that opioid receptors and a high opioid tone influences cholestatic pruritus (Bergasa, Schmitt et al. 1998). A study on patients with PBC showed a significant effect on the course of the disease and itch intensity by adding bezofibrate, an agonist to peroxisome proliferator-activated receptors, in combination with ursodeoxycholic acid (Corpechot, Chazouillères et al. 2018). In another double-blind randomised placebo-controlled trial in 2021 on moderate to severe pruritus, 74 patients with a variety of chronic cholestatic liver diseases were treated with bezofibrate (400 mg/day), resulting in a significant improvement of itch compared to placebo (de Vries, Bolier et al. 2021).

A series of studies investigated the effect of inhibition of the ileal bile acid transporter (IBAT). In the most recent study, Mayo and coworkers investigated the effect of treatment with maralixibat on 66 patients with severe cholestatic pruritus (Mayo, Pockros et al. 2019). Maralixibat did not result in an improvement of itch exceeding that reached with placebo. In contrast, treatment with odevixibat, another IBAT inhibitor, in children with severe cholestatic liver disease resulted in a significant reduction of itch (Baumann, Sturm et al. 2021, Thompson, Arnell et al. 2022). Odevixibat is licensed for the treatment of patients with progressive familial intrahepatic cholestasis and pruritus in Europe.

4.2.3. Pruritus in metabolic and endocrine diseases

In endocrine disorders such as hypo- or 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); its pathophysiology, however, remains speculative. These patients often experience a lack of vitamin D and minerals (e.g. zinc, etc.), which might contribute to CP. Iron deficiency may also be associated with CP (Adams 1989, Saini, Jain et al. 2021). 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 in diabetes mellitus may occur (Labib, Rosen et al. 2022). The clinical picture is not specific, frequently accompanied by dry skin and sometimes showing chro-

nic secondary scratch lesions (IFSI III) (Weisshaar and Dalgard 2009).

4.2.4. Pruritus in connective tissue diseases

CP can also be a significant symptom in (autoimmune) connective tissue diseases such as lupus erythematodes, dermatomyositis (DM), Sjögren's syndrome and fibromyalgia, adding burden to these diseases. A study reported that 76.8% of patients with cutaneous lupus experienced pruritus, with its intensity correlating with disease activity (Samotij, Szczęch et al. 2021). This suggests that pruritus in lupus may even serve as an indicator of disease activity. In DM, recent research indicated that tumour necrosis factor-α (TNF-α) and IL-6 play a central role in DM-associated itch, correlating with disease activity and pruritus severity (Vincze, Herczeg-Lisztes et al. 2023). In another study, 51% of DM patients suffered from itch, with increased expression of IL-31 in lesional skin (Kim, Zeidi et al. 2018).

In Sjögren's syndrome, pruritus is usually associated with xerosis cutis and can also be a bothersome symptom (André and Böckle 2022). According to recent studies, fibromyalgia, although primarily characterised by chronic pain, is also associated with CP in 3–29% of patients (Laniosz, Wetter et al. 2014, Karaosmanoğlu, Cetinkaya et al. 2024). Interestingly, it was reported that fibromyalgia might exacerbate CP and vice versa, pointing to a proportionate relationship observed in some of these patients (D'Onghia, Ciaffi et al. 2024).

4.2.5. Pruritus in malignancy

Several malignant disorders including tumours, bone marrow diseases, as well as myeloproliferative and lymphoproliferative disorders, may be accompanied by pruritus. The term "paraneoplastic pruritus" is used to describe pruritus in patients with solid cancer or haematological malignancies (Yosipovitch 2010, Weisshaar, Weiss et al. 2015). This also includes severe cases of CPG. Ovarian cancer was reported in CPG, with the latter completely healing after cancer treatment and no relapse thereafter (Steffens, Kaplan et al. 2023).

The true prevalence of this symptom in malignant diseases is unclear and epidemiological data in this field are limited (Larson, Tang et al. 2018). 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 caused pruritus (Kilic, Gul et al. 2007). Most of the patients affected do not exhibit specific dermatoses, but instead unaffected skin or non-specific eruptions with or 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's lymphoma, around 15–50% in non-Hodgkin's lymphoma and around 15–50% in PV (Weisshaar, Weiss et al. 2015, Tefferi, Vannucchi et al. 2018). In a cohort study of 327,502 patients and 327,502 matched controls, patients with undifferentiated pruritus had an increased risk of being diagnosed with a haematological cancer in the first year. Clinicians should consider a thorough review of symptoms and assessment of cancer risk factors when deciding on work-up for patients presenting with undifferentiated pruritus (Deng, Parthasarathy et al. 2022).

The mechanisms of pruritus in malignancy are still not well 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 effect on the brain or nerves (in brain tumours), the latter being referred to as neuropathic pruritus (Bernhard 1994, Zylicz, Twycross et al. 2004). IL-31, a T helper (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). Various non-histaminergic mediators such as tryptase and IL-31 could be explored as novel therapeutic targets for managing pruritus in mycosis fungoides patients (Hu, Scheffel et al. 2024). In PV, more than 50% of patients suffer from CP (Egli, Wieczorek et al. 1988, Diehn and Tefferi 2001, Tefferi, Vannucchi et al. 2018) with aquagenic pruritus and pinching sensations after contact with water being a characteristic but not obligatory 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 immunoglobulin E (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 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. This related in particular to haematological cancers, above all Hodgkin's lymphoma (Johannesdottir, Farkas et al. 2014); however, the study was unable to differentiate between acute and chronic itch.

4.2.6. Pruritus in systemic infectious diseases (+ COVID-19)

Acute or chronic pruritus may occur with skin infections and infestations with ecto- or endoparasites, among which scabies is the most prominent example (Serling, Leslie et al. 2011). Oxyuriasis usually induces intense anal pruritus, which in women might also involve the genital area. In onchocerciasis, severe pruritus is also a dominant and early symptom. Viral infections such as herpes simplex, herpes zoster and varicella can present with acute pruritus. CP may occur in 4% of herpes zoster patients, upon which it is termed post-herpetic itch (Weisshaar and Dalgard 2009).

Some generalised infections are also 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 a 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 strong 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). Small-fibre neuropathies are frequently observed in pruritic disorders like HIV or HCV infections (Sène 2018).

CP in COVID-19 was reported as "COVID-19 pruritus", "vaccine-associated pruritus" or "post-COVID-19 pruritus" as well as "face mask-induced pruritus". However, there is no clear evidence of a causal relationship between COVID-19 and CP. (Sameni, Hajikhani et al. 2020, Stefaniak, Białynicki-Birula et al. 2020, Szepietowski, Matusiak et al. 2020, Al-Ansari, Al-Sharari et al. 2021, Doyle and Watchorn 2022, Labib, Nattkemper et al. 2022, Martora, Villani et al. 2022, Shafie'ei, Jamali et al. 2022).

4.2.7. Pruritus in neurological diseases

Neuropathic pruritus is typically associated with the presence of various paraesthetic sensations, including a feeling of electrical current, prickling, tingling, burning and numbness (Misery, Brenaut et al. 2014).

Space-occupying lesions (herniations, tumours, abscesses, haemorrhage) of the nervous system and degenerative neurological diseases, e.g. neuromyelitis optica spectrum disorders and multiple sclerosis (MS), 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, He, Wu et al. 2020, Fardel, Brenaut et al. 2022, Misery, Genestet et al. 2022, Saini, Gunasekaran et al. 2023). 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). Pruritus in MS patients is most frequently localised to the extremities, face or scalp and is suggestive of an increased risk of experiencing MS-related symptoms (Ingrasci, Tornes et al. 2023). Entrapment syndromes of specific nerve roots 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). Recent evidence suggests that scalp dysesthesia, a specific clinical entity, should be included in this list (Ju, Vander Does et al. 2022, Lee, Morillo-Hernandez et al. 2023). A recognised clinical phenomenon is generalised pruritus triggered by a localised neurological disorder, e.g. brachioradial pruritus (Kwatra, Ständer et al. 2013, Zeidler and Ständer 2014). A typical sign of brachioradial pruritus, and occasionally also in other forms of neuropathic pruritus, is the ice-pack sign. Patients use extreme cold to relieve itch, while it may be worsened by warmth.

Small-fibre neuropathies are neuropathies involving epidermal nerve endings. In this case, pruritus is a major symptom and usually begins in the palms and soles (Misery, Bodere et al. 2014, Brenaut, Marcorelles et al. 2015, Sène 2018). Pruritus in several systemic diseases associated with small-fibre neuropathy is similarly included, the list being led by diabetes (Brenaut, Marcorelles et al. 2015, Sène 2018). Other causes of small-fibre neuropathies include autoimmune diseases, excessive alcohol or tobacco, vitamin deficiency and some genetic diseases (Fouchard, Brenaut et al. 2023).

In a broader perspective, small-fibre neuropathies 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). A very frequent cause of mild pruritus is sensitive skin, which may be considered as low-noise small-fibre neuropathy (Wollenberg and Giménez-Arnau 2022).

4.2.8. 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 compared to non-depressed individuals (Dalgard,

Lien et al. 2007) and that the severity of itch increases with symptoms of depression among adolescents (Halvorsen, Dalgard et al. 2009); as those studies are cross-sectional, the association between itch and depression is bi-directional.

In a small pilot study, 40 adult depressed patients in a psychiatric clinic were examined. Seven (17.5%) had itch. In all affected cases, the itching disappeared when the depressive symptoms improved. On the other hand, the itching reappeared when the depressive symptoms worsened again (Pacan, Grzesiak et al. 2009). This suggests a strong (biological) connection between the two symptoms in the corresponding subgroup of depressed patients. A recent smaller study demonstrated that itch was more prevalent among patients with psychiatric disease (Norman, Guenther et al. 2023).

Another recent study compared CP patients with no known psychiatric comorbidities with a group of patients with somatoform pruritus (ICD-10: F54) or psychological factors in the aetiology or course of CP (ICD-10: F45.0 or F45.8). This subgroup was significantly younger and more often female, single, divorced or widowed. Among other things, they described their itch as being localised deep inside and painful, and they reported a higher number of triggers increasing their itch (Misery, Alexandre et al. 2007, Schneider, Grebe et al. 2020).

The pathophysiological background seems to correlate with the 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 (also referred to as delusional infestation), a rare condition that is challenging to treat, both for dermatologists and psychiatrists (Lepping, Huber et al. 2015). A similar disorder is Morgellons disease, but here patients complain of invasion of the skin by inanimate objects such as fibres or particles (Kemperman, Vulink et al. 2024). Some authors link this disease to Lyme's disease, while others view it as a variant of delusional infestation. Overall, the psychiatric population is little studied with regard to skin symptoms, but likely psychiatric morbidity contributes to the pathophysiology of CP even in the absence of skin disease (Pereira, Kremer et al. 2016). On the other hand, CP might result in exhaustion, depression and anxiety, making it sometimes difficult to distinguish whether pruritus is the cause or the result of psychological problems or diseases.

4.2.9. 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 deposition in the skin have also been suggested, but the pathogenesis of drug-induced pruritus 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).

Long-term pruritus has also been reported in breast cancer patients treated with trastuzumab and pertuzumab: Approximately 5% of patients treated with this combination suffered from pruritus that was localised mainly on the upper extremities and which lasted for several months to years in some cases (Gu, Dusza et al. 2024). Other anti-cancer monoclonal antibodies, such as programmed cell death (PD-1) inhibitors, can also induce CP in patients with melanoma, breast, colorectal or lung cancer (Wang, Chen et al. 2017, Wang, Kong et al. 2020).

4.3. Specific patient populations

4.3.1. Chronic pruritus in females and males

Currently, there are only few studies available comparing CP between women and men. Men are usually older at onset of CP compared to women. In an analysis of the underlying aetiologies, females had more neuropathic and somatoform diseases underlying CP, while males had more dermatoses and systemic diseases. Females show more CPG and men non-lesional skin in CP. Females report higher itch intensities and have higher scores in QOL assessments (Ständer, Stumpf et al. 2013, Ständer, Pogatzki-Zahn et al. 2015). Data regarding sex differences in the intensity and skin flare of histaminergic itch under standardised conditions are conflicting (Magerl, Westerman et al. 1990, Stumpf, Burgmer et al. 2013, Hartmann, Handwerker et al. 2015). In one study using functional MRI, differences in central itch processing were observed (Mueller, Mueller et al. 2019), but it remains unknown whether such differences are biologically based or rather socially learned gender behaviour.

Regarding itch therapy, there are some important sex differences to consider. For example, women have more adverse drug reactions and have higher plasma levels of several drugs used in itch treatment such as antidepres-

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, meropenem, 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, sitagliptin
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 stimulants	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, oestrogens, exemestane, 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
Tranquilisers	Alprazolam, chlordiazepoxidd, lorazepam, oxazepam, prazepam
Uricostatics	Allopurinol, colchicine, probenecid, tiopronin
Bruton's tyrosine kinase inhibitors	Zanubrutinib
Antimalarials	Hydroxychloroquine, chloroquine, amodiaquine, halofantrine
Alkaloids	Atropine, papaverine
Anticoagulants	Ticlopidine
Targeted anticancer drugs	Cetuximab, erlotinib, panitumumab, vermurafenib, pembrolizumab, nilotinib, gefitinib, ipilimumab, rituximab
Biologics (other than anticancer)	Adalimumab, infliximab
Retinoids	Isotretinoin, alitretinoin
Analgesics	Morphine, codeine, tramadol

sants or immunosuppressive drugs (Schmid, Navarini et al. 2019).

Chronic vulvar pruritus is estimated to occur in 5–10% of the women reporting itch in the German population. This condition affects QOL among women of all ages and is often caused by lichen sclerosus, a common chronic inflammatory disease (Weisshaar 2015, Woelber, Prieske et al. 2019).

4.3.2. Chronic pruritus in the elderly

Only a small number of studies have investigated CP in the elderly (Aboeldahab, Khalil et al. 2021). They are characterised by selection bias and differing endpoints (pruritic skin disease or itch). A recent prospective observational study found a prevalence of CP in 23.4% of geriatric patients (Günther, Kobus et al. 2025). A cross-sectional study from Egypt reports that CP in elderly patients was generalised among 73%, 35% had moderate severity and 20% had winter exacerbation. A dermatological aetiology was found in 54% and a systemic aetiology in 30% of the cases (Aboeldahab, Khalil et al. 2021). A cross-sectional study from Poland among elderly patients hospitalised in a geriatric ward showed that 35% were affected by CP (Reszke, Białynicki-birula et al. 2019). A Turkish study in 4099 elderly patients found that pruritus was the most common skin symptom, affecting 11.5% of patients. 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).

4.3.3. Chronic pruritus in pregnancy

A recent study mentions a point prevalence of pruritus of 20%, while pruritus prevalence during the entire pregnancy was 38% (Szczech, Wiatrowski et al. 2017). These figures are higher than previous observations, with an estimation of pruritus as the leading dermatological symptom in around 18% of pregnancies (Weisshaar, Diepgen et al. 2005). It can present as specific dermatoses of pregnancy (polymorphic eruption of pregnancy [PEP], pemphigoid gestationis [PG], 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 in five consultations for pruritus in pregnancy is not related to the specific dermatoses 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 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).

4.3.4. Chronic pruritus in children

There are only a limited number of epidemiological studies assessing the prevalence of CP in children (Weisshaar, Diepgen et al. 2005, Weisshaar and Dalgard 2009). In an observational study of German primary school children, CP was reported with a point prevalence of 14.7% (Theodosiou, Nissen et al., 2022). The spectrum of differential diagnoses 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 severity of pruritus in AD and sleeplessness (Staab, Diepgen et al. 2006, Weisshaar, Diepgen et al. 2008). Chronic spontaneous urticaria (CSU) is a reason for CP in approximately 3% of children (Gaig, Olona et al. 2004). Recently, a European survey of management approaches in chronic urticaria in children concluded that the large variation in diagnosis and treatment emphasises the need to re-evaluate guidelines in chronic urticaria patients (Tsabouri, Arasi et al. 2022).

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 and also in children suffering from psoriasis that is bothersome and impacts their daily life (Lim, Chan et al. 2008, Reich, Trybucka et al. 2008, Mannix, Edson-Heredia et al. 2021).

In children 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 on 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 on the families' QOL include the dermatitis family impact questionnaire (Lawson, Lewis-Jones et al. 1998). A new set of validated and feasible instruments shows promise in quantifying itch severity and QOL in older children, namely TweenItchy QOL and Itchy Quant (Kong, Francois et al. 2021). The course of advanced learning for the management of itch task force recommend a multidisciplinary and multidimensional approach for paediatric CP (Metz, Wahn et al. 2013).

It must be assumed that non-dermatological systemic causes of CP in children are mostly based on genetic diseases or systemic diseases, e.g. biliary atresia or hypoplasia, familial hyperbilirubinemia syndromes, or CKD (Weisshaar and Dalgard 2009, Wojtowicz-Prus, Kilis-Pstrusinska et al. 2016, Gurnani, Miloh et al. 2021, Pratyusha, Dawman et al. 2021, Reszke, Kilis-Pstrusinska et al. 2021). A cross-sectional study in children with end-stage renal disease who underwent dialysis showed that the likelihood of having a more severe pruritus score was associated with an increased level of serum calcium and higher age (Mehrkash, Golestaneh et al. 2021). Also, 22% of children with type-1 diabetes showed itch limited to a few regions of the body, usually the upper limbs (50%) and trunk (31.8%) and associated with impaired QOL (Stefaniak, Zubkiewicz-Kucharska et al. 2020). 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

History and clinical examination are key to clarifying the aetiology of pruritus, which in turn is the only means of ensuring adequate treatment. A number of typical features in the patient history may be helpful and sometimes even diagnostic to finding the cause of pruritus, e.g. duration of pruritus, localisation, time course, triggering factors, as well as information in the personal and family history. To obtain this information in a structured manner, we find it helpful to ask the following questions: "When?", "where?", "why?", "what?", "who?", "whom?" ("*6 Ws*") and "how does itch feel?".

1 ***When* did itch start, and *when* exactly does it itch?** (onset, duration, minimum, maximum, temporal variations)
   - Onset/duration of pruritus: Answering these questions allows differentiation between acute pruritus (less than 6 weeks) and CP (6 weeks or more). Intermittent itching can be a symptom of CSU. In patients with factitial urticaria, itch typically starts as localised itch that might generalise with scratching. Constant itching is typical for internal diseases, e.g. renal or cholestatic pruritus or itch

in patients with malignant lymphoma.

- Maximum and minimum of pruritus (circadian and/or seasonal variation): Nocturnal generalised pruritus in association with chills, fatigue, tiredness and B symptoms (weight loss, fever and nocturnal sweating) is suggestive of malignancy such as Hodgkin's disease. Seasonal pruritus in wintertime ("winter pruritus") is found in exsiccation eczema in the elderly and often in patients with AD or psoriasis.

2 ***Where* does it itch?** (localisation)
Differentiation between localised and generalised pruritus is not only important to narrow down differential diagnoses but also to tailor treatment strategies.

Localised pruritus can be caused by itchy dermatosis when itch occurs at sites where primary lesions were already present at itch onset. Localised itch on primarily non-inflamed skin is suggestive for neurological disease, especially when it appears in an asymmetrical pattern (Oaklander 2011, Oaklander 2012, Stumpf and Ständer 2013, Cohen, Andrews et al. 2014, Brenaut, Marcorelles et al. 2015): Unilateral localised 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). CP might also be associated with internal diseases, where it can occur at typical sites, e.g. on the back in CKD-aP (Ponticelli and Bencini 1995) or in the anogenital region in patients with diabetes mellitus (Neilly, Martin et al. 1986, Wahid and Kanjee 1998). Localised vulvar pruritus can also be a symptom of iron deficiency (Stäubli 1981). Pruritus on palms and soles is typical for cholestatic pruritus.

Generalised pruritus can be caused by itchy dermatoses even if the inflamed skin does not show generalised spread, e.g. in patients with psoriasis (Yosipovitch, Goon et al. 2000). Generalised pruritus, however, is highly suggestive and typical for internal diseases (Polat, Oztas et al. 2008) or use of a drug that causes itch. In one study, in contrast, generalised pruritus was found more frequently in patients with dermatoses than in pruritus due to systemic disease (Weisshaar, Apfelbacher et al. 2006).

3 ***Why* does it itch?** (triggering/provoking factors)
Trigger factors, including psychosocial factors (stressful life factors, e.g. economic difficulties), and the relationship between pruritus and specific activities can be important: CP during physical activity can reflect cholinergic pruritus and cholinergic urticaria. CP provoked by the skin cooling after emerging from a warm shower/bath can be a sign of aquagenic pruritus, polycythaemia vera or xerosis cutis. Pruritus can also be triggered by skin contact with external factors including irritants (e.g. excessive use of soaps or disinfectants) and/or allergens, the latter resulting in immediate (e.g. latex hypersensitivity) or delayed-type skin reactions (e.g. contact dermatitis to nickel, fragrances, preservatives). Pruritic immediate or delayed-type reactions can also be triggered by numerous drugs, leading to CP in chronic use. Usually, these reactions are accompanied by typical features of drug eruptions (immediate type: urticaria, erythema, possibly angioedema and systemic reactions/anaphylaxis; delayed type: maculopapular rash and others). Pruritus as part of such a drug eruption needs to be distinguished from other forms of drug-induced CP mentioned in Sect. 4.2.8.

Based on these considerations, meticulous history-taking is necessary to capture potential topical and/or systemic itch-inducing or -aggravating factors.

4 ***What* (pre-existing) diseases does the patient have** (dermatological and non-dermatological conditions, e.g. depression and anxiety, medication) **and *what* have they already tried in order to reduce itch?** (personal strategies, treatment)

- **Pre-existing dermatological conditions:** The identification of pre-existing skin diseases in the patient history is crucial, especially if CP on primarily inflamed skin is assumed. In such cases a history of AD, psoriasis or lichen planus suggests that itch has occurred due to an exacerbation or persistence of the known disease. An atopic background should always be verified or excluded. An atopic disposition may be the only explanation for the onset of itch in patients with PUO. Thus, the most important question to classify pruritus is "How did the skin look when itch first appeared?": If itch first appeared on primarily diseased (inflamed) skin, itchy dermatosis – which needs to be diagnosed – is causative. If itch appeared on normal looking skin ("itch 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).
- **Internal diseases:** Knowledge of pre-existing internal diseases (e.g. chronic kidney disease, cholestatic liver disease, diabetes or iron deficiency) is of particular importance if pruritus on primarily non-inflamed skin is assumed. Unfortunately, there are no defined laboratory cut-off values (e.g. blood creatinine levels) that are indicative for the causative pruritogenic role of an internal disease.
- **Pre-existing medication:** History taking must include documentation of medication use and change of medications in the previous 12 months before the CP started. Drugs known to provoke pruritus are listed in Table 2. In patients with pre-

vious surgery and infusion treatments, HES must be considered as a trigger of CP.

- **Previous antipruritic treatment**: Exploration of local and/or systemic treatments used may provide additional diagnostic information and help to select and tailor future treatment. For example, responsiveness to antihistamines may help to distinguish between histaminergic and non-histaminergic itch. Previous treatment with topicals should be explored to assess steroid responsiveness and under- or overtreatment with topical glucocorticosteroids (GCs), also to identify corticosteroid concerns ("corticophobia") or overuse of topical GCs. Likewise, "intolerance" to topical calcineurin inhibitors may be explored and clarified as the usual initial burning due to TRPV1 activation. Previous treatment-related side effects, such as sedation by antihistamines and gabapentinoids or the wide range of potential side effects of gabapentinoids, opioids, tri- and tetracyclic antidepressants as well as selective serotonin reuptake inhibitors (SSRIs) should also be explored.

5 *Who* is affected by itch (apart from the patient)?

If multiple family members are affected by the onset of itch, scabies or other ectoparasitoses should be considered. Moreover, thorough assessment of the patient's family history may reveal familial skin diseases and/or internal disorders that are accompanied by itch.

6 With *whom* has the patient had contact?

A history of unprotected sexual contacts might expand differential diagnoses of chronic itch to sexually transmitted diseases associated with pruritus, such as pubic lice, HIV or syphilis. Itch associated with cutaneous contact with animals could be indicative of allergic contact dermatitis (immediate or delayed-type) or unrecognised zoophilic dermatophytic infections.

7 *How* does itch feel?

The experience of itch reported by the patient provides important information with regard to intensity and quality of the symptom. Currently, several validated assessment tools that are regularly used in clinical routine and study protocols are available to address itch intensity. Besides intensity, the quality of the symptom (itch, burning and stinging, etc.) does not fluctuate and is usually assessed via itch questionnaires (Ständer, Augustin et al. 2013, Pereira and Ständer 2017, Pereira and Ständer 2019).

- **Intensity of itch** *(How intense is the itch?)* This parameter is most representative for the symptom and might also correlate with other dimensions of the symptom, such as scratching intensity, sleep disturbance and disease burden. Monodimensional scales are preferable over multidimensional scales, where unequivocal determination of the itch severity might be difficult.
- Among the monodimensional scales, the VAS and NRS (0=no itch, 10=worst itch imaginable) are the gold standard. They usually assess the average or worst itch intensity over the preceding 24 h. The worst NRS 24 h, also called worst itch (WI) or peak pruritus (PP), is currently most frequently used in clinical trials as a validated endpoint. For example, at a baseline pruritus of NRS 7, a drop of 4 points on this scale is currently considered a meaningful improvement (Ständer, Augustin et al. 2013, Reich, Riepe et al. 2016, Reich, Chatzigeorkidis et al. 2017, Storck, Sandmann et al. 2021, Topp, Apfelbacher et al. 2022).
- **Quality of itch**: Quality of itch (burning, painful, stinging, prickling) is best quantified with special tools that have been developed for the assessment of pruritus (Weisshaar, Kupfer et al. 2024).

Clinical examination

Clinical examination of the patient should always include a thorough inspection of the entire skin, including scalp, nails, oral cavity and anogenital region. Of utmost importance is the distinction between primary and secondary skin lesions. This makes it possible to distinguish the three main 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's history, these have been present since itch onset, pruritus on primarily diseased (inflamed) skin can be diagnosed (IFSI group I). Further investigations can be performed to specify the underlying dermatosis, including skin biopsy, microbiological investigations and, in certain cases, laboratory testing (e.g. IgE, indirect immunofluorescence).

Secondary skin lesions include excoriations, ulcerations, necrosis, crusts, papules, nodules, lichenifications, atrophy, scars as well as hyper- and hypo-pigmentation of the skin. In patients with CP, these are most likely caused by scratching. If a patient with CP reports that no skin lesions were visible at the onset of itch, pruritus on primarily non-diseased (non-inflamed) skin should be diagnosed (IFSI group II). Internal disease, medications, pregnancy and neurological or psychiatric conditions will be causative. Laboratory and radiological investigations, adapted to the patient history and pre-existing diseases, are mandatory to obtain a final diagnosis. In the case that no underlying cause can be found, the provisional diagnosis chronic PUO may apply.

If a patient presents with extensive, characteristic nodular, excoriated or lichenified scratch lesions that have persisted for months or years (e.g. prurigo nodules), pruritus with chronic secondary scratch lesions (IFSI group III) can be diagnosed. The underlying cause(s) may be dermatologic, systemic, neurological, psychiatric and/or drugs. Skin biopsy, laboratory and radiological investiga-

tions, as well as procedures adapted to the patient history and pre-existing diseases, will lead to a final diagnosis.

The categorisation of patients into only one of the three IFSI groups is not always possible since many patients might have several of the itch-inducing and/or aggravating factors mentioned above, as well as clinical overlaps of IFSI groups I–III (e.g. nummular eczema, CKD and chronic scratch lesions).

In addition to inspecting the whole integument, a general physical examination should be performed in all patients with unclear pruritus, including palpation of abdominal organs and lymph nodes, as well as a rectal examination. **Expert recommendation:** We recommend taking a detailed history of each patient with CP. 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 also recommend performing a complete dermatological and at least a focused general physical examination.

5.2. Diagnostic algorithm and diagnostics

Laboratory screening, clinical/technical approaches and investigations are summarised in **Tables 3** and **4** including a diagnostic algorithm (**Fig. 1**).

5.3. Measuring and scoring of pruritus

Measuring pruritus in all its dimensions is a challenge since it is a purely subjective sensation. Intensity, severity, localisation, course or scratching behaviour need to be considered for a comprehensive assessment (Ständer, Augustin et al. 2013). The intensity is a representative parameter for the overall character of pruritus and can be used as a monitor parameter in daily clinical practice and in clinical trials. The NRS, VAS and the Itch Severity Scale (ISS; (Majeski, Johnson et al. 2007)) were reported to be used for pruritus intensity and severity. The NRS and the VAS can easily be used to assess pruritus intensity. Both scales are validated for CP and use a range of 0 (no pruritus) to 10 (worst imaginable pruritus). They can assess worst or average pruritus during the preceding 24 h.

Next to monodimensional scales, other instruments are available with varying methodological quality (Topp, Apfelbacher et al. 2022), as summarised in **Table 12**. A systematic review investigated and compared several instruments for measuring pruritus with the aim of recommending instruments for the different aspects of pruritus (intensity, severity, duration, QOL (Topp, Apfelbacher et al. 2022)). The authors recommended the use of the ISS for pruritus severity and the ItchyQOL for pruritus-related health-related quality of life (HRQOL), as these instruments had the highest methodological

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

Approach I	• Detailed personal and family history: preceding skin changes and/or allergies/atopy? • Weight loss, fever, night sweats, fatigue? • Emotional stress, depression, anxiety, psychiatric disorders? • Travel history? • Unprotected sexual contacts? • Occupation, pets/animals? • Medication, drug abuse? • Complete skin examination and physical examination including lymph node and rectal examination • Pay attention to subtle primary skin disorders: xerosis, "well-groomed" scabies, pre-bullous bullous pemphigoid • Consider performing a skin biopsy if primary and/or secondary skin lesions are present or if "invisible" dermatosis is suspected (including direct immunofluorescence, for example if an autoimmune bullous disease, lupus or vasculitis is considered possible) • **Consider general measures according to Table 5**
First-step lab screening	• Differential blood cell count, ESR • Creatinine, urea • Transaminases (ASAT, ALAT), AP, γ-GT, (in)direct bilirubin • LDH • TSH • HbA1c, fasting glucose • Ferritin, CRP **If findings are pathological, consider detailed work-up according to Table 4** **If findings are inconclusive and CP persists, proceed to "Approach II" and "Further investigations"**
Approach II	• Renew detailed history • Repeat detailed general physical examination • Additional laboratory testing as indicated under "Further investigations" below • Screening for parasites (stool microscopy or stool PCR, blood serology) • Chest X-ray: lymphadenopathy, chronic infections, neoplasia? • Abdominal ultrasound: lymphadenopathy, neoplasia, hepatobiliary, renal, pancreatic or splenic pathology/neoplasia? • Reconsider the diagnostic benefit of a (second) skin biopsy if primary and/or secondary skin lesions are present or if "invisible" dermatosis is suspected (including direct immunofluorescence, for example if an autoimmune bullous disease, lupus or vasculitis is considered possible)
Further investigations	• Serum protein electrophoresis and immunofixation • Hepatitis B,C screening • Calcium, parathormone • Swab for candida in the case of genital and/or oral mucocutaneous pruritus • Serum-tryptase (imaging studies and bone marrow investigation for mastocytosis if indicated) • Urine: mast cell metabolites **If findings are pathological, consider detailed work-up according to Table 4**

See abbreviations and explanations (page 2).

Table 4. Laboratory and technical investigations in chronic pruritus due to systemic diseases. To interpret laboratory results and/or to determine the most suitable imaging technique, specialists may be consulted

Metabolic and endocrine diseases	
Renal insufficiency	Lab I: Creatinine (and urea for elderly) Lab II: Calcium, phosphate, parathormone, hydrogen carbonate, urinalysis with urine protein concentration. ANA, anti-ds-DNA-Ab, ANCAs, anti-GBM-Ab, etc. Imaging: Sonography of the kidneys, CT or MRI
Liver diseases with or without cholestasis	Lab I: ALAT, ASAT, γ-GT, AP, HBV and HCV serology Lab II: Bilirubin, LDH, AMA, ASMA, AAA, ANA, ANCA Imaging: Sonography of the liver, CT or MRT, (MRC or ERC to rule out primary sclerosing cholangitis)
Hyperparathyroidism	Lab II: Only if serum calcium is elevated Calcium, parathormone phosphate, vitamin D (1,25-vitamin D, 25-vitamin D) Imaging: Sonography of the parathyroid glands, scintigraphy, MRI
Hyper- and hypothyroidism	Lab I: TSH Lab II: FT3, FT4, thyroid peroxidase antibody; thyroglobulin antibody; TSH receptor antibody Imaging: 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, soluble transferrin receptor, transferrin, TSAT Imaging: Gastrointestinal endoscopy
Malabsorption	Lab tests only in the 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), anti-transglutaminase antibodies Imaging: Endoscopy with biopsy
Other diseases	
Pruritus of the elderly	Lab I: Differential blood count, creatinine, urea, eGFR, ALAT, ASAT, AP, TSH, consider malnutrition (body mass index, albumin, total cholesterol, zinc, vitamin D)
Infectious diseases	In the case of clinical suspicion and/or history of high-risk sexual contacts: Screening for HIV, hepatitis B and C. In the case of clinical suspicion due to history and/or when eosinophilia was found in differentiated blood count: Stool culture, PCR and microscopic examination for parasites or blood serology
Haematological disorders	**Myeloproliverative disease** Lab I: Blood count (elevated haematocrit and haemoglobin, increase of red blood cells, leukocytosis, thrombocytosis), ESR Lab II: To rule out secondary erythrocytosis: EPO, *JAK2* V617F, cytogenetic testing, bone marrow aspiration etc. Imaging: Abdominal sonography, CT or MRI **Lymphoma** Lab I: Blood count, ESR Lab II: Direct biopsy or extirpation of suspected lymph nodes, bone marrow, flow cytometry Imaging: Sonography, thoracoabdominal CT or MRI **Multiple myeloma** Quantitative measurement of serum immunoglobulins and light chains. Bone marrow aspiration etc.
Neurological diseases	In the case of suspected neurological disorder (e.g. neuropathic components such as tingling, paraesthesia, electrifying sensations, ice-pack sign): Gloves and socks distribution of dysaesthesia/hypaesthesia: **Sensory polyneuropathy:** Touch sensation tests (e.g. monofilament), vibratory sensation test, tendon reflex testing, electroneuro- and myography, lab screening according to neurologist. If all are unremarkable: Consider small-fibre neuropathy **Small-fibre neuropathy:** Quantitative sensory testing (vibration, cold, warmth, heat pain, and cold pain) Skin biopsy to determine IENFD, methodology (according to Pereira, Derichs et al. 2020) **Multiple sclerosis** Lab: Cerebrospinal fluid analysis (oligoclonal bands?) Imaging: MRI (CT) of brain **Brain tumours** Lab: Cerebrospinal fluid analysis with histopathology Imaging: MRI (CT) of brain **Notalgia paraesthetica** MRI of thoracic spine **Brachioradial pruritus** MRI of thoracic and cervical spine
Psychiatric or psychosomatic diseases	Psychiatric assessment, questionnaires for depressive and anxiety disorders may be helpful and include PHQ-8 (depression), GAD-7 (anxiety), SSS-8, SSD-12 and HADS.
Pregnancy with or without cholestasis	Lab I: ASAT, ALAT, AP, γ-GT Lab II: Bile acids, bilirubin, serology for HAV, HBV, HCV, EBV and CMV, autoimmune screen for chronic active hepatitis and primary biliary cholangitis (ASMAs and AMAs) (Girling 2006) Imaging: Liver ultrasound
Paraneoplastic	Consider consultation with an oncologist, haematologist or palliative care specialist
Drug-induced pruritus	Lab I: Eosinophilia, γ-GT, AP, bilirubin, AST, ALAT, LDH Skin biopsy in the case of HES exposure (electron microscopy)

See abbreviations and explanations (page 2).

quality. However, NRS and VAS are most commonly used in daily clinical practice.

The German pruritus questionnaire was developed and validated in CP patients in 2024, giving access to a multimodal assessment of pruritus in its entirety and pruritus-related QOL. It records localisation, course, intensity, quality, patient history data on the general state of health, sociodemographic data, QOL and coping

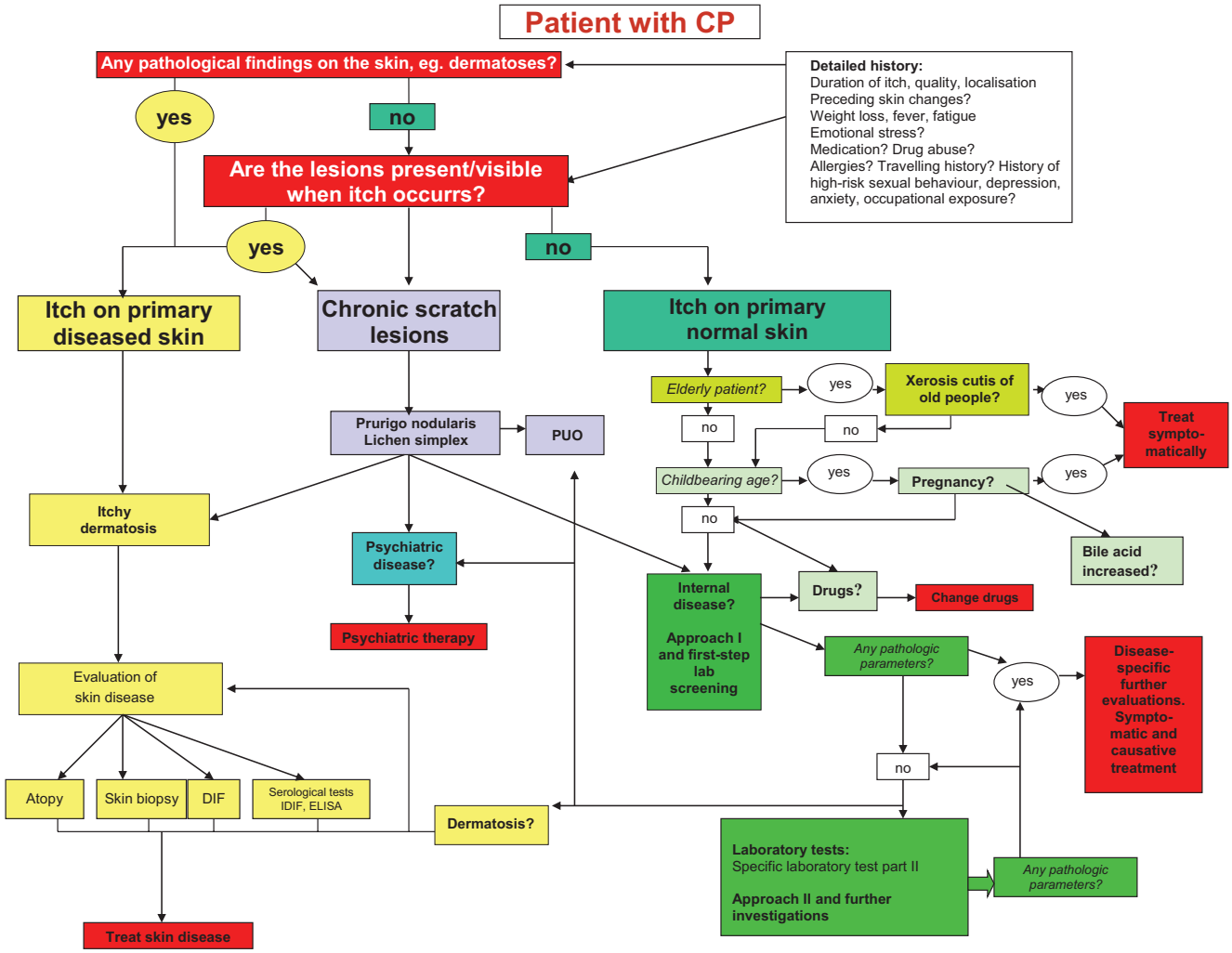

Fig. 1. Diagnostic algorithm. See abbreviations and explanations (page 2).

methods (Weisshaar, Kupfer et al. 2024). It is composed of seven modules – history, pruritus-specific history, pruritus-specific therapy, sleep, pruritus-specific QOL, IFSI classification and Charlson comorbidity score – and takes 25–35 min to complete.

Expert recommendation: We recommend assessing the intensity of itch using the NRS or VAS (worst or average intensity of itch in the preceding 24 h)

5.4. Quality of life in pruritus

CP as a chronic stressor has a major impact on patients' HRQOL. It impacts mood, QOL and self-assessment of patients (Weisshaar, Apfelbacher et al. 2006, Dalgard, Svensson et al. 2020), often being associated with insomnia, depression, anxiety and HRQOL impairment (Ständer, Pereira et al. 2024). In qualitative interviews, CP patients reported their pruritus as uncontrollable and life-defining (Bathe, Weisshaar et al. 2013). Trouble concentrating at work as well as feelings of shame and social isolation accompanied CP. A large European multicentre study observing dermatological patients showed significant differences between patients with itchy dermatoses, patients without itch and controls regarding depression, anxiety, suicidal ideation, QOL and economic difficulties (Dalgard, Svensson et al. 2020). Women report a higher intensity and higher burden of CP than men (Kursewicz, Fowler et al. 2020).

The burden of CP differs between diagnoses, with pruritus of dermatological origin having the highest impact on patients' QOL (Weisshaar, Apfelbacher et al. 2006). In a large multicentre study regarding dermatological disease, PN patients reported the highest pruritus intensity and impact on QOL compared with other diagnoses (Steinke, Zeidler et al. 2018).

CP can significantly impact HRQOL of patients in a primary and secondary way. The burden of CP is in itself stressful or exhausting, but can also lead to scratch-related lesions, which can have social implications and increase the burden (Ferreira, Katamanin et al. 2024). In a study of patients with pruritic dermatoses, patients suffering from CP reported more feelings of stigmatisation,

stress, anxiety and depression, possibly leading them to isolate themselves (Zeidler, Kupfer et al. 2024).

Measurement of QOL in CP is of great importance. Especially in multimorbid patient populations with several QOL-impairing factors present, a differentiated measurement of pruritus-related QOL needs to be performed. The ItchyQOL (Desai, Poindexter et al. 2008) has already been used for this purpose in large patient populations (Weiss, Mettang et al. 2016). It is validated in English, German, French, Italian, Polish, Russian, Spanish and Turkish (Zeidler, Steinke et al. 2019).

Expert Recommendation: We recommend using the ItchyQOL to assess QOL in pruritus patients.

6. THERAPY

6.1. Therapy: general principles

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 prevent dryness of the skin. Controlled studies on damaged skin (eczema or dry skin in haemodialysis patients) have shown reduction of itch after treatment with emollients as monotherapy, probably through improvement of the skin barrier (Hawley, Lio et al. 2023, Magnolo, Jaenicke et al. 2023, Nevols, Watkins et al. 2023). However, the evidence from controlled studies on the efficacy of emollients on normal-appearing skin is lacking. The question is whether tactile stimulation of the skin by pressure while applying emollients sooths itch.

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 CP and atopic skin (Yosipovitch, Duque et al. 2007, Pfab, Valet et al. 2010). Also, lukewarm baths with colloidal oatmeal may restore the skin barrier and sooth pruritus (Lisante, Nuñez et al. 2017). Daily use of moisturisers preserves the skin barrier and prevents dryness. Several active supplementary ingredients with anti-itch properties may be used in moisturisers suitable for dry skin (see below, Sect. 6.3.1).

Table 5. General measures for treating chronic pruritus

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, moisturising syndets and shower/bath oils
	Skin moisturiser on a daily basis, especially after showering and bathing
	Luke-warm water, bath (max. 20 min), dabbing the skin dry
	Ointments, creams/lotions/emollients/sprays (especially at night) with, e.g. urea, camphor, menthol, polidocanol, cooling wet or fat-moist wraps
	In erosive/excoriated scratch lesions: occlusive patches and/or dressings
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 irritant substances (e.g. compresses with rivanol, chamomile, tea-tree oil)
	Specific airborne allergens in sensitised atopic patients, e.g. house dust mites
Relaxation techniques	Autogenic training, relaxation therapy, psychosocial education
Education	Educational training programmes for coping with the vicious itch-scratch-itch cycle (Staab, Diepgen et al. 2006, Weisshaar, Diepgen et al. 2008, Bathe, Matterne et al. 2009), keeping finger nails short

Prior to further symptomatic therapy, the patient should undergo a careful diagnostic evaluation, as well as treatment for any underlying disease (Tables 3 and 4, Fig. 1). Pharmacologic interventions for specific pruritic diseases, e.g. AD and urticaria, should be performed according to the current guideline for 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, Zuberbier, Aberer et al. 2018).

If pruritus persists, consecutive or combined step-by-step symptomatic treatment is necessary (see **Table 10**). Before considering systemic treatment, patients' adherence to topical treatment, including skin care, needs to be ensured (Simon and Bieber 2014). Severe generalised CP often requires a multi-modal treatment approach. Treatments may be administered alone or in different combinations and sometimes repeated.

In selected cases, medical devices for the relief of pruritus may be considered (Sect. 6.4.12).

Almost all therapies used to treat CP are not approved for this indication and can only be prescribed "off-label", which might require separate informed consent and cost coverage by the insurer.

6.2. Causative therapy and aetiology-specific treatment

Whenever possible, the underlying disease of CP should be treated. In addition, avoidance of contact allergens

and discontinuation of implicated drugs are important. Normally, there is significant relief of pruritus when the underlying disease improves, e.g. when Hodgkin's disease responds to chemotherapy or when a patient with PBC has undergone liver transplantation. 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 of the underlying diseases. For only a few of these treatments can evidence of efficacy be found in controlled studies. Treatments for CP in specific diseases are presented in **Tables 6–9**. When deciding the choice of treatment, consideration should be given to the level of evidence, side effects, practicability, costs, availability of a treatment and individual factors such as patient age.

6.3. Topical therapy

Doxepin and topical mast cell inhibitors, which were included in the previous guideline, have been excluded in this update as they were no longer deemed relevant to the treatment of CP.

6.3.1. Emollients and moisturisers

Pruritus in AD, ichthyosis, diabetes and CKD is often linked to dry skin. Patients report that smoothing and rehydrating dry skin reduce pruritus. In an experimental model, the number of sensory non-myelinated nerve fibres in the epidermis was increased in mice with itchy, dry skin compared with healthy controls, while disruption of the epidermal barrier resulted in spontaneous scratching (Miyamoto, Nojima et al. 2002, Andoh, Asakawa et al. 2018). Thus, an intact skin barrier is essential for its sensorial properties. An impaired skin barrier may be restored by the use of emollients or moisturisers

Table 6. Therapeutic options in chronic kidney disease (CKD)-associated pruritus

Therapeutic options in CKD-associated pruritus	
Antipruritic effects in controlled studies	• Activated charcoal 6 g/day (Bernhard 1994) • Gabapentin 300 mg 3x/week post-dialysis (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 post-dialysis (Wikstrom, Gellert et al. 2005) • Thalidomide 100 mg/day (Silva, Viana et al. 1994) • Montelukast 10 mg/day (Mahmudpour, Roozbeh et al. 2017) • Difelikefalin 0.5 mg/kg i.v. after dialysis (Fishbane, Jamal et al. 2020, Yosipovitch, Awad et al. 2023) – license applied for in Europe • Sertraline initial dose 25 mg daily (Chan, Li et al. 2013, Elsayed, Elgohary et al. 2023) • Doxepin 10 mg twice daily (Pour-Reza-Gholi, Nasrollahi et al. 2007)
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/day (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./day (Bernhard 1994) • Ketotifen 1–2 mg/day (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 primary biliary cholangitis!) (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, Dijk et al. 2012) • Odevixibat (10–200 µg/kg oral daily for 4 weeks) (Baumann, Sturm et al. 2021) in children with cholestatic pruritus • Naltrexone 50 mg/day (Wolfhagen, Sternieri et al. 1997, Terg, Coronel et al. 2002) • Naloxone 0.2 µg/kg BW/min (Bergasa, Alling et al. 1995) • Nalmefene 20 mg 2x/day (Bergasa, Alling et al. 1999) • Sertraline 75–100 mg/day (Mayo, Handem et al. 2007, Ataei, Kord et al. 2019) • Thalidomide 100 mg/day (McCormick, Scott et al. 1994) • For fibrosing cholangiopathies: bezafibrate 400 mg daily (de Vries, Bolier et al. 2021)
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 2.5 µg once daily (Yagi, Tanaka et al. 2018) • Phenobarbital 2-5 mg/kg BW/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 s.c. 2x/week (Epstein and Kaplan 2004) • Nasobiliary drainage (Appleby, Hutchinson et al. 2015) • Plasma perfusion (Fleischer 2000) • Extracorporeal albumin dialysis with 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)

See abbreviations and explanations (page 2).

Table 8. Therapeutic options in polycythaemia vera

Therapeutic options in polycythaemia vera	
Effects shown in controlled trials	• Ruxolitinib (JAK inhibitor) 2x10 mg/day (Vannucchi, Kiladjian et al. 2015, Passamonti, Griesshammer et al. 2017, Gisslinger, Klade et al. 2020, Koschmieder, Isfort et al. 2023)
Effects shown in case reports	• Paroxetine 20 mg/day (Diehn and Tefferi 2001, Tefferi and Fonseca 2002) • Hydroxyzine (Diehn and Tefferi 2001) • Fluoxetine 10 mg/day (Tefferi and Fonseca 2002) • Aspirin (Fjellner and Hagermark 1979) • Cimetidine 900 mg/day (Easton and Galbraith 1978, Weick, Donovan et al. 1982) • Pizotifen 0.5 mg 3x/day (Fitzsimons, Dagg et al. 1981) • Cholestyramine (Chanarin and Szur 1975) • UVB phototherapy (Baldo, Sammarco et al. 2002) • Photochemotherapy (PUVA) (Swerlick 1985, Jeanmougin, Rain et al. 1996) • Transcutaneous electrical nerve stimulation (Tinegate and McLelland 2002) • Interferon-alpha (de Wolf, Hendriks et al. 1991, Finelli, Gugliotta et al. 1993, Muller, de Wolf et al. 1995, Taylor, Dolan et al. 1996)

Table 9. Therapeutic options in idiopathic aquagenic pruritus

Effects confirmed in case reports (Steinman and Greaves 1985, Wolf and Krakowski 1988, Shelley and Shelley 1998)	• Topical capsaicin 0.025%–1% thrice/day 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, Morgado-Carrasco, Riera-Monroig et al. 2020) • Propranolol 10–80 mg/day (Nosbaum, Pecquet et al. 2011) • Atenolol 25 mg/day (Cao, Yong et al. 2015) • Clonidine 0.1 mg twice/day • Astemizol 10 mg/day • Ibuprofen (prior to bathing) • Pregabalin 150–300 mg/day • Antihistamines, e.g. hydroxizine 25 mg/day, chlorpheneramin 8 mg/day, cetirizine, loratadine, fexofenadine, terfinadine • H2 blockers: cimetidine 900 mg/day • Opioid receptor antagonists, e.g. naltrexone 25–50 mg/day (Phan, Bernhard et al. 2010) • Selective serotonin reuptake inhibitors, e.g. paroxetine 20 mg/day, fluoxetine 10 mg/day • Interferon-alpha 2b 5x3 million IE 1st week, 3x3 million IE 2nd–4th week • Omalizumab (Murphy, Duffin et al. 2018, Kaur, Jabbal et al. 2022) • β-Alanine supplementation (Friedlander and Admani 2021)

(Lodén 2012). These two terms are often used synonymously, but there is a difference. Emollients consist of varying amounts and different types of lipids which have an occlusive effect and reduce transepidermal water loss, thereby enhancing stratum corneum hydration (Lodén 2003). They are available as lotions, creams and ointments. Moisturisers additionally contain humectants, low molecular substances, with the capability to attract water into the stratum corneum (Lodén 2003). Both lipids and humectants may have anti-inflammatory and antipruritic properties (Purnamawati, Indrastuti et al. 2017).

Table 10. 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 antihistamines*, topical corticosteroids
Step 2	• Symptomatic causative-adapted therapy **(Tables 6–9)** 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 antihistamines, 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.

The effects of moisturisers containing 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 to have weak 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-aP and PUO (Szepietowski, Szepietowski et al. 2005, Ständer, Reinhardt et al. 2006, Eberlein, Eicke et al. 2008), A vehicle-controlled study with 100 subjects did not show any significant difference between the lotion with and without PEA regarding itch intensity (Visse, Blome et al. 2017).

Allergenic compounds (e.g. fragrances or preservatives) and irritant substances (e.g. surfactants) in emollients and moisturisers should be avoided. In the case of a sudden deterioration of itch or appearance of dermatitis, contact allergy should be excluded by patch testing with a baseline series that includes several preservatives, fragrance mixes, Compositae mixes and lanolin (Uter, Bauer et al. 2021).

Expert recommendation: We recommend the use of moisturisers for the treatment of CP. We recommend the use of emollients or moisturisers for dry skin in CP patients.

6.3.2. 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-aP, 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 of LA in the short term (or symptomatic) treatment of localised forms of pruritus such as

notalgia paraesthetica and anal pruritus has been reported in case series and open-label studies (Layton and Cotterill 1991, Weisshaar, Heyer et al. 1996, Mülkoğlu and Nacır 2020). Topical preparations (creams, lotions, patches) of lidocaine, alone or in combination with other active substances (e.g. the LA prilocain), may be used safely for short-term periods (1–3 times daily for up to 4 weeks), to treat localised forms of CP (limited to 10% of target body surface area).

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, either 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 (2 times daily for up to 4 weeks) has been shown to ameliorate CKD-aP 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, ceramides) (Young, Patel et al. 2009, Zirwas MJ 2017).

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 short-term (1–3 times daily for up to 4 weeks) application of topical LA to be used as an additional symptomatic therapy for CP.

6.3.3. 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 as well as its favourable safety profile, there is only scarce literature on its efficacy. Prescriptions of zinc are frequently used, with concentrations varying from 10–50% in creams, liniments, lotions, ointments and pastes that are useful to treat localised pruritus, in children as well as in adults (Welsh 1955). Calamine, which is often found in soothing liniments and dressings, contains 98% zinc oxide (Welsh 1955) and 2% ferric oxide. In an experimental study, zinc oxide was shown to be as effective as moderate potency corticosteroid in suppressing contact dermatitis (Wallengren 2011). In a survey-based recall study with 52 patients suffering from CPG, 37 patients were treated with zinc dressings as monotherapy, 46% of whom reported a positive effect on pruritus (Todberg, Zachariae et al. 2020).

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 transient receptor potential (TRP) cation channel subfamily M (melastatin) member 8 (TRPM8) receptor (Green and Schoen 2007), which belongs to the same TRP family of excitatory ion channels as TRPV1, the capsaicin receptor. It is thought to also ameliorate pruritus by activating spinal B5-I interneurons, which inhibit pruriceptive afferents (Pereira and Lerner 2014). 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 also 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 for CP and CPG.

6.3.4. Capsaicin

Capsaicin (trans-8-metyl-N-vanillyl-6-nonenamide) is the pungent agent of chilli peppers and is used as a pain- and itch-relieving medication by activation of TRPV1 receptors resulting in calcium influx, depolarisation and release of neuropeptides such as substance P (SP) (Andersen, Marker et al. 2017). TRPV1 receptors are expressed in diverse cell types including neurons, keratinocytes and immune cells (Szolcsanyi 2004, Cevikbas and Lerner 2020, Zhou, Zhang et al. 2022). 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 desensitisation 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). Capsaicin has been shown to act independently of mast cells and to reduce non-histaminergic itch better than histaminergic

itch (Wallengren and Hakanson 1992, Andersen, Marker et al. 2017).

The greater the initial dose of capsaicin and the more frequent the applications, the sooner desensitisation 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 subsequent tachyphylaxis, 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 (0.025–0.075% 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).Capsaicin 8% has been shown to reduce nonhistaminergic itch better than histaminergic itch (Andersen, Marker et al. 2017).

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 CKD-aP (Breneman, Cardone et al. 1992, Tarng, Cho et al. 1996, Yeam, Yo et al. 2021). Case reports and case series described effects in HES-induced pruritus (Szeimies, Stolz et al. 1994, Reimann, Luger et al. 2000), CPG (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 post-herpetic neuralgia and HIV neuropathy have been evaluated in a Cochrane review (Derry, Sven-Rice et al. 2013).

Expert recommendation: We recommend topical capsaicin for localised forms of CP and CPG.

6.3.5. Topical glucocorticosteroids

Topical GCs 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 inflamed skin. Once- or twice-daily application(s) 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 (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 GCs and should be closely monitored (Patel and Yosipovitch 2010, Chi, Kirtschig et al. 2017).

In an 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 merely an indirect anti-inflammatory effect (Curto, Carnero et al. 2014).

Some studies suggest that topical corticosteroids such as betamethasone valerate are effective in PN (Saraceno, Chiricozzi et al. 2010, Siepmann, Lotts et al. 2013). Intra-lesional 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 GCs in CP associated with inflammatory dermatoses and CPG. We recommend against topical GCs in CP on non-inflamed skin.

6.3.6. Tacrolimus and pimecrolimus

The effects of the topical calcineurin inhibitors (TCIs) tacrolimus and pimecrolimus on pruritus are mediated both by their immunological and 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 an antipruritic effect on individual patients with CP (Leslie, Greaves et al. 2015). TCIs are highly effective against pruritus in AD, and in contrast to topical corticosteroids do not induce skin atrophy (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, with 0.03% tacrolimus and 1% pimecrolimus cream (Cury Martins, Martins et al. 2015). Clinical trials have shown a benefit for 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 CKD (Pauli-Magnus, Klumpp et al. 2000, Kuypers, Claes et al. 2004). Despite early reports of efficacy of tacrolimus on CKD-aP, these observations have not been confirmed in a controlled study and, thus, 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 routine TCI use, in children as well as adults (Cury Martins, Martins et al. 2015, Luger, Boguniewicz et al. 2015, Luger, Paller et al. 2021). 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 alcohol consumption; however, this can be blocked with acetylsalicylic acid (500 mg) taken in advance of drinking alcohol (Wollenberg, Oranje et al. 2016). A systematic review and meta-analysis reported an association between TCI use and risk of lymphoma, but no other cancers (Siegfried, Jaworski et al. 2013). The risk of lymphoma associated with long-term use of TCIs has been estimated to be very low, as shown in prospective and meta-analytic studies in both paediatric and adult patients (Lam, Zhu et al. 2021). However, the authors concluded that "combined with the low absolute risk of lymphoma, the potential increased risk attributable to TCI use for any individual patient is likely very small". 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 localised forms of CP and CPG.

6.4. Systemic therapy

6.4.1. Antihistamines

Antihistamines are the most widely used systemic antipruritic drugs in dermatology (Leslie 2013). Histamine and its receptors (H1R–H4R) play a significant role in the progression and modulation of histamine-mediated cutaneous diseases (Thangam, Jemina et al. 2018). Drugs that target the H1 receptor can effectively block the acute itch of cutaneous conditions such 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 induces impaired sleep, interfering with the rapid eye movement (REM) phase. A prospective cohort study recently suggested that its cumulative long-term use (in combination with other anticholinergic drugs) is associated with an increased risk of dementia (Gray, Anderson et al. 2015). First-generation antihistamine poses substantial risks to older adults, including cognitive impairment, falls, confusion, dry mouth and constipation, but is still prescribed at higher rates in primary and specialist care (Cenzer, Nkansah-Mahaneyn et al. 2020). Due to these side effects, the use of sedative antihistamines is limited nowadays 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 inverse agonists offer 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 platelet activating factor (PAF) receptors, has been shown to significantly reduce the severity of pruritus alone, in mastocytosis, as well as mosquito bite and urticaria in both adults and children (Mullol, Bousquet et al. 2015, Hide, Suzuki et al. 2019, Hide, Suzuki et al. 2019). In adult patients with confirmed mosquito-bite allergy, rupatadine 10 mg administered prophylactically has been shown to be effective in reducing subsequent hive and skin pruritus (Karppinen, Brummer-Korvenkontio et al. 2012). Bilastine is highly selective for the H1 receptor, showing

rapid onset, prolonged duration of action, no need for dose adjustment and low potential for central nervous system (CNS) impairment or drug–drug interaction (Wang, Lim-Jurado et al. 2016). Bilastine demonstrated favourable outcomes in real-world experience in any pruritus associated with inflammatory skin conditions (Lynde, Sussman et al. 2020). Antihistamines are effective to treat acute spontaneous urticaria and CSU (Phinyo, Koompawichit et al. 2021). Intravenous cetirizine was statistically non-inferior to intravenous diphenhydramine to control pruritus in acute urticaria (Abella, Berger et al. 2020), and it has been also shown that the addition of dexamethasone to chlorpheniramine was not better than antihistamine alone to control severe pruritus in acute urticaria (Palungwachira, Vilaisri et al. 2021). European guidelines on urticaria (Zuberbier, Aberer et al. 2018, Zuberbier, Abdul Latiff et al. 2021) recommend second-generation anti-H1 antihistamines as the first-line therapy for CSU, starting at licensed doses and being increased to up to four times the dose if licensed doses fail to control the disease. The use of increased doses of antihistamine has shown a good safety profile (Cataldi, Maurer et al. 2019). Systemic H1 antihistamines are often employed to treat pruritus in AD. Few randomised controlled trials showed only a weak or no effect in decreasing pruritus. A Cochrane review did not find consistent evidence that H1 antihistamines are effective as an "add-on" therapy for AD when compared to placebo (Matterne, Böhmer et al. 2019). Nevertheless, fexofenadine probably leads to a small improvement in patient-assessed pruritus with no significant differences in the amount of treatment used to prevent eczema flare-ups. The older, sedating H1 antihistamines commonly used by dermatologists in AD (Garg, Zhao et al. 2021) may be more useful for this indication especially in acute AD flare-ups, 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 antihistamine 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, Mueller, Navarini et al. 2020, Schaper-Gerhardt, Rossbach et al. 2020).

Antihistamines are widely used as first-line drugs for the treatment of CP associated with various systemic diseases such as chronic renal failure, cholestasis, haematopoietic 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 and 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, Zuberbier, Abdul Latiff et al. 2021). 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). ZPL-3893787, an H4 receptor antagonist, recently showed a weak effect in controlling pruritus versus placebo (Werfel, G. et al. 2018). There is pre-clinical evidence that local antagonism of the H3 receptor can induce scratching; therefore, new drugs that target the H3 receptor are anticipated in the field, with the hope that more effective treatment of CP 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 symptomatic therapy of CP.

6.4.2. Mast cell inhibitors

Ketotifen (1 mg twice daily) showed antipruritic effects in patients with CKD-aP, but less so 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 and CPG.

6.4.3. Glucocorticosteroids

Systemic 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. GCs 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 GCs 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). In a small study with lichen planus patients, oral mini-pulse treatment with betamethasone 3 mg weekly for 12 weeks resulted in a complete resolution of pruritus in 95% of patients (Alsakaan, Abd-Elsalam et al. 2022).

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 severe 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 RCTs, 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-aP (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/day) 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 for nalfurafine in patients with CKD-aP (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 an 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.

Mathur and colleagues (Mathur, Kumar et al. 2017) reported on the effectiveness of nalbuphine, a μ-opioid antagonist and κ-opioid agonist, in 371 haemodialysis patients with chronic itch in two different dosages (60 mg and 120 mg orally per day). While 120 mg nalbuphine achieved a significant improvement of pruritus on an NRS (0, no itching; 10, worst possible itching) of 3.5 compared to placebo (2.8), treatment with 60 mg

did not result in better itch control than did placebo. At present, nalbuphine is not licensed for the treatment of CKD-associated itch in Europe.

Another large placebo-controlled clinical study in 378 haemodialysis patients reported a significant reduction in WI by the highly restricted κ-agonistic drug difelikefalin at 0.5 μg per kg body weight for 12 weeks (Fishbane, Jamal et al. 2020). Side effects were mild, mostly involving nausea and dizziness. Difelikafalin has been approved for the treatment of uraemic itch in several countries in Europe. In a recent study on safety and efficacy of difelikefalin, various doses of the drug were compared in Japanese haemodialysis patients with moderate to severe CKD-aP. In this double–blind, four-arm study, difelikefalin proved to be efficient at a dose of 0.5 and 1.0 μg/kg body weight and best tolerated at the dose of 0.5 μg/kg body weight (Narita, Tsubakihara et al. 2022).

In a phase 2 study with 269 haemodialysis- and non-haemodialysis-dependent CKD-aP patients, oral difelikefalin (1 mg) once daily for 12 weeks resulted in a Worst Itch Numeric Rating Scale (WI-NRS) of 0–1 in 39% of patients paralleled with an improvement in itch-related QOL measures by approximately 20% (Yosipovitch, Awad et al. 2023).

In another phase 2 study with 126 patients suffering from notalgia paraesthetica, difelikefalin resulted in a modestly greater itch reduction than placebo after 8 weeks at 2 mg twice/day (Kim, Bissonnette et al. 2023). However, itch-related QOL did not differ between the groups. Side effects occurred more frequently in the difelikefalin group with headache, dizziness, constipation and increased urine output being the most common of these. Difelikefalin was also tested in a phase 3 study, but primary endpoints were not met and research was discontinued in notalgia paraesthetica.

Expert recommendation: We recommend the use of κ-opioid agonist difelikefalin in CKD-aP. We suggest κ-opioid agonistic drugs such as nalfurafine or nalbuphine in CKD-aP. We suggest μ-opioid receptor antagonists in CP, especially in cholestatic pruritus and CKD-aP.

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 post-herpetic 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 for gabapentin (Mendham 2004, Gray, Kirby et al. 2011). Double-blind RCTs were performed for CKD-aP (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). Gabapentin may be used topically in CKD-aP (Aquino, Luchangco et al. 2020).

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 for pregabalin in patients on haemodialysis within 1 month (Aperis, Paliouras et al. 2010). In another study on uraemic itch, treatment with 75 mg 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 PN 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-aP led to a significant improvement of pruritus in both groups, but was significantly more effective in patients receiving pregabalin (Foroutan, Etminan et al. 2017, Ishida, McCulloch et al. 2018). In a head-to-head study, daily 25 mg pregabalin was compared to 100 mg gabapentin p.o. in 90 hemodialysis patients suffering from CKD-aP. Pregabalin proved to be somewhat more efficient but with more side effects such as nausea and dizziness (Khan, Wahaj et al. 2022).

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: The use of gabapentin and pregabalin was associated with much higher hazards of altered mental status, falls and fractures (Ishida, McCulloch et al. 2018).

The prescription of pregabalin is restricted in some countries (e.g. France) due to its potential use as a recreational drug and the possible induction of hallucinations.

In a placebo-controlled pilot study with epidermolysis bullosa patients, topical gabapentin 10% did not show a significant effect on pruritus after a treatment duration of 6 weeks (Saki, Vahedi et al. 2022).

Expert recommendation: We recommend gabapentin and pregabalin in neuropathic CP and in CKD-aP. We suggest gabapentin and pregabalin for refractory CP of miscellaneous origin such as CPUO or CPG.

6.4.6. Antidepressants

Systematic reviews show evidence that antidepressants are particularly effective in refractory pruritus, pruritus in CKD, cholestasis and neoplasm (Kouwenhoven, van de Kerkhof et al. 2017), as well as in other forms of CP (Brasileiro, 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 14% of dermatological patients with acute or chronic pruritus (Dalgard, Svensson et al. 2020), demonstrating 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, Reszke and Szepietowski 2019).

The antipruritic action of 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). Paroxetine (20 mg/day) has exhibited antipruritic effects in pruritus due to PV (Tefferi and Fonseca 2002), paraneoplastic pruritus (Zylicz, Smits et al. 1998, Weisshaar 2008), psychiatric disease (Biondi, Arcangeli et al. 2000, Heisig, Salomon et al. 2012) and pruritus in palliative care patients at a very low dose (5 mg/day, (Kraut 2017)). 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, Ataei, Kord et al. 2019) and children (Thébaut, Habes et al. 2016), as well as in CKD-aP (Shakiba, Sanadgol et al. 2012, Chan, Li et al. 2013). In a double-blind RCT among 50 haemodialysis patients, sertraline was shown to be effective in reducing CKD-aP (Pakfetrat, Malekmakan et al. 2018). Similarly, in a recent double-blinded, placebo-controlled study with 60 patients, sertraline 50 mg twice daily for 8 weeks resulted in a significant improvement in pruritus (Elsayed, Elgohary et al. 2023). In a study with 38 patients with psoriasis and psychological comorbidities, escitalopram (10–20 mg/day) improved the scores for anxiety and depression and also reduced itch severity (D'Erme, Zanieri et al. 2014) (**Table 11**).

Tricyclic antidepressants exert their effect via several mechanisms, such as serotonin and noradrenalin reuptake inhibition and postsynaptic receptor antagonism against H1, alpha1 as well as muscarinic and serotonin receptors (Reszke and Szepietowski 2019).

Tricyclic antidepressants like doxepin have been effective in urticaria, pruritus due to sulphur mustard exposure, UP and scalp pruritus (Shohrati, Davoudi et al. 2007, Brasileiro, Barreto et al. 2016, Foroutan, Etminan et al. 2017, Chan, Reddy et al. 2020, Haber, Bachour et al. 2020). Doxepin may be administered in a dose from 25 to 100 mg/day (Reszke and Szepietowski 2019). Amitriptyline 25 mg/day and doxepin have shown a reduction in pruritus in patients with brachioradial pruritus (Shohrati, Tajik et al. 2007, Wachholz, Masuda et al. 2017).

The tricyclic antidepressant doxepin showed antipruritic effects when applied as a 5% cream in double-blind studies for the treatment of AD (Drake, Fallon et al. 1994), lichen simplex, nummular dermatitis and contact dermatitis (Drake and Millikan 1995). A meta-analysis showed that there is a lack of evidence to suggest that doxepin is an effective treatment in pruritus after burn injuries (McGovern, Quasim et al. 2021). Doxepin does not seem useful in UP (Feng, Yuan et al. 2020). 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).

Mirtazapine (tetracyclic antidepressant) 15–45 mg/day is an atypical antidepressant, both noradrenergic and serotonergic, and has been shown to be effective in the treatment of CP in case series with patients with AD, lichen simplex, adenocarcinoma, nodular sclerosis, Hodgkin´s disease, large B-cell lymphoma, chronic lymphocytic leukemia, breast cancer, advanced renal cell carcinoma and pruritus associated with carcinoma en cuirasse (Davis, Frandsen et al. 2003, Demierre and Taverna 2006, Lee, Girouard et al. 2016, Khanna, Boozalis et al. 2019), as well as in a before–after clinical trial and a crossover randomised clinical trial with patients

Table 11. Recommendations and suggestions regarding antidepressants for the treatment of itch in different diseases

Antidepressant	Indication
Paroxetine	Paraneoplastic, chronic PUO, AD, Hodgkin's disease, non-Hodgkin's lymphoma, rectal carcinoma, CPG, *PV, psychogenic, pruritus in palliative care, diabetes mellitus-associated itch*
Fluvoxamine	AD, Hodgkin's disease, non-Hodgkin's lymphoma, rectal carcinoma, CPG, *diabetes mellitus-associated itch*
Sertraline	Cholestatic pruritus, CKD-associated pruritus
Escitalopram	*Psoriasis*
Doxepin	*Urticaria*, pruritus due to sulphur mustard exposure, *CKD-aP, scalp pruritus, brachioradial pruritus, HIV-associated itch*
Amitriptyline	*Brachioradial pruritus*
Mirtazapine	CKD-aP, *AD, lichen simplex, adenocarcinoma, nodular sclerosis, Hodgkin´s disease, large B-cell lymphoma, chronic lymphocytic leukaemia, advanced renal cell carcinoma, breast cancer, pruritus associated with carcinoma en cuirasse*

Italic = weaker studies (cases, case series, inconsistent results).
See abbreviations and explanations (page 2).

Table 12. Selected measurement instruments and their psychometric properties

Name of instrument	Patient-reported outcomes	Validity	Reliability	Languages[8]
GPQ[1]	Pruritus intensity, severity, HRQOL, coping with pruritus, pruritus localisation	++	+/++	German
Mean itch NRS (24 h)[2]	Pruritus intensity	+++	++/+++	English, German, Polish, Japanese
Worst itch NRS (24 h)[3]	Pruritus intensity	++	++	English, German, Polish
Mean itch VAS (24 h)[2]	Pruritus intensity	+++	++/+++	English, German, Polish
Worst itch VAS (24 h)[4]	Pruritus intensity	++	+++	English, German, French
ItchyQuant[5]	Pruritus intensity	+++	+	English
ISS[6]	Pruritus severity	++	++/+++	English, Danish, Korean, Spanish
5-D Itch Scale[7]	Pruritus severity	++	+/+++	English, Arabic, Urdu

Annotations: [1](Weisshaar, Kupfer et al. 2024); [2](Phan, Blome et al. 2012); [3](Verweyen, Ständer et al. 2019); [4](Pedersen, McHorney et al. 2016); [5](Haydek, Love et al. 2017); [6](Majeski, Johnson et al. 2007); [7](Elman, Hynan et al. 2010); [8](Topp, Apfelbacher et al. 2022)

undergoing haemodialysis (Gholyaf, Sheikh et al. 2020, Mehrpooya, Gholyaf et al. 2020).

Side effects of antidepressants are common and include drowsiness, fatigue and headache, mostly initially, but cardiovascular and gastrointestinal symptoms also 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, fluvoxamine, sertraline, escitalopram, doxepin, amitriptyline, mirtazapine) for psychogenic CP, paraneoplastic CP, cholestatic CP and brachioradial CP. We suggest selected antidepressants for refractory CP of miscellaneous origin, such as CKD-aP, CPG and AD, particularly if anxiety and/or depression and/or sleep deprivation are associated.

6.4.7. 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 TNF-α (Arrese, Dominguez-Soto et al. 2001).

The best results with thalidomide in CP have been achieved in PN showing a rapid decrease in pruritus on thalidomide (50–300 mg/day) (Winkelmann, Connolly et al. 1984, Johnke and Zachariae 1993). In a 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 very recent small study of 17 patients confirmed good response to low dosage (50–100 mg) in recalcitrant PN. None of the patients developed neuropathy (Sardana, Gupta et al. 2020). 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-aP 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). However, lenalidomide was also reported to cause pruritus (Shahda, Loehrer et al. 2016). More studies are needed to evaluate the effectiveness and tolerability of this thalidomide analogue.
Expert recommendation: We suggest thalidomide only for selected cases of refractory severe CP after informing the patient about teratogenicity and the dose-related risk of neuropathy.

6.4.8. Leukotriene receptor antagonists

Leukotriene receptor antagonists (e.g. montelukast) 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). Two RCTs, one with 16 patients and the other with 80 patients, observed significant improvement of CKD-aP with montelukast (Nasrollahi A. 2007, Mahmudpour, Roozbeh et al. 2017).
Expert recommendation: We suggest leukotriene receptor antagonists for the treatment of CKD-aP.

6.4.9. Cyclosporine, methotrexate and azathioprine

Controlled clinical studies investigating the efficacy of systemic anti-inflammatory drugs on CP are scarce. Cyclosporine was used early on 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 toxi-

city 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). In a clinical study on 42 patients with AD-associated pruritus, 21 were treated with cyclosporine (3.5–5 mg/kg/day) and 21 with NB-UVB (Jaworek, Szafraniec et al. 2020). In this study, 12-week cyclosporine treatment was less effective than NB-UVB, the WI VAS being reduced from 9.5 to 6.9 (compared with 9.4 to 4.0 for NB-UVB).

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 2–4 weeks of treatment (Berth-Jones, Smith et al. 1995, Siepmann, Luger et al. 2008, Wiznia, Callahan et al. 2018). 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).

In a recent study on 81 PN patients, 69 received NB-UVB (thrice weekly), 26 received methotrexate (15–25 mg weekly) and 16 received cyclosporine (2.5–5 mg/kg/day). The improvement at week 16 was significant (35%, 31% and 38%, respectively) defined as a numerical rating scale of 0–3 or no/mild itching (Taghaddos, Savinova et al. 2024).

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 CPG, 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 another retrospective study on 16 patients with CPG treated with 15–20 mg methotrexate once weekly, 31% reported reduction of pruritus (Todberg, Zachariae et al. 2020). In a multicentre 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). In a case series of six patients with CPG who did not respond sufficiently to methotrexate (10–20 mg/week), combination treatment with alitretinoin (10–30 mg/day) resulted in near-complete clinical remission in five patients (Bergqvist, Fiani et al. 2021). In a small study with lichen planus patients, oral methotrexate 7.5 mg weekly for 12 weeks resulted in a complete resolution of pruritus in 78% of patients (Alsakaan, Abd-Elsalam et al. 2022).

Azathioprine, licensed as a corticosteroid-sparing drug for blistering diseases, has proved effective in pruritus associated with bullous pemphigoid at 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). A retrospective review reported on 96 patients with life-altering CP who had previously responded to systemic steroids. 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).

A recent meta-analysis of 39 RCTs on systemic treatments in adult patients with AD concluded that high-dose cyclosporine is more effective at improving itch and QOL when compared to azathioprine and methotrexate (Sesi and Feldman 2024).

Data on systemic treatment with tacrolimus in CP are sparse. Besides case reports (Halvorsen and Aasebø 2015), one open-label study on 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 for CPG. We cannot make a recommendation with respect to tacrolimus for refractory CP associated with inflammatory dermatoses and for CPG.

6.4.10. Neurokinin 1 receptor antagonist

In neurogenic inflammation, the neuropeptide SP is released from cutaneous sensory neurons into the tissue and binds to the neurokinin 1 receptor (NK1R) and MAS-related G protein-coupled receptor X2 (MRGPRX2) on mast cells, keratinocytes and blood vessels. SP promotes neurogenic inflammation and mast cell degranulation. Accordingly, inhibition of the pruritogenic effects of SP by blocking the corresponding receptor is an antipruritic approach. Several case series and case reports suggested a positive role for the NK1R antagonist aprepitant in

CP, e.g. cutaneous T-cell lymphoma, solid tumours, drug-induced pruritus, CP with atopic predisposition and CPG (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). Recent controlled trials showed conflicting results. Some randomised double-blind placebo-controlled phase 2 studies using topical or systemic aprepitant or serlopitant failed to show a benefit compared to placebo in chronic prurigo and epidermolysis bullosa (Lönndahl, Holst et al. 2018, Ohanyan, Schoepke et al. 2018, Ständer, Kwon et al. 2019, Tsianakas, Zeidler et al. 2019 [Epub ahead of print]).

In a recent randomised phase 2 study with 130 patients suffering from epidermal growth factor receptor tyrosine kinase inhibitor-induced pruritus, aprepitant resulted in a better and faster improvement in pruritus compared to desloratadine (Zhou, Zhang et al. 2022).

NK1R antagonists are currently not in pharmaceutical development for the treatment of pruritus. However, in certain patients, they have convincing effects according to expert opinion.

Expert recommendation: We suggest NK1R antagonists such as aprepitant in refractory CP of miscellaneous origin such as CPG.

6.4.11. Biologics

In recent years, biologics have significantly transformed the treatment landscape for CP by targeting specific cytokines and pathways involved in the pathophysiology of itch. Their efficacy in relieving itch has primarily been demonstrated in chronic inflammatory skin diseases such as AD, PN, psoriasis and urticaria. Numerous biologics have been approved for these conditions when treatment with topical and conventional systemic drugs has proven insufficient.

This section mainly focuses on the efficacy of these biologics in reducing pruritus in these four conditions. For this purpose, itch-related study endpoints are summarised in **Table 13**, along with corresponding disease severity endpoints. For other important aspects, such as (off-label) indications, side effects and safety issues related to the discussed biologics, we refer the reader to the relevant guidelines, which are cited below where suitable.

Atopic dermatitis

The efficacy of biologics in reducing pruritus in AD patients has been evaluated in various clinical trials. Dupilumab, a monoclonal antibody that binds IL-4Rα and inhibits signalling of both IL-4 and IL-13, has shown significant efficacy in these AD patients: In the SOLO 1 and 2 (Simpson, Bieber et al. 2016), AD ADOL (Simpson, Paller et al. 2020), and LIBERTY AD CHRONOS (Blauvelt, de Bruin-Weller et al. 2017) trials, dupilumab resulted in an itch reduction within 1 week that progressively improved and was sustained through to the end of follow-up, up to 1 year (Silverberg, Yosipovitch et al. 2020). Head-to-head trials involving dupilumab and JAK inhibitors are discussed in Sect. 6.4.12.

Tralokinumab, an IL-13 inhibitor, has also been proven to relieve pruritus in AD patients. The ECZTRA 1, 2 and 3 trials (Wollenberg, Blauvelt et al. 2021) evaluated the efficacy of tralokinumab in treating moderate-to-severe AD, including its impact on pruritus over a 52-week period. According to the data from these trials, tralokinumab demonstrated significant and sustained improvements in pruritus, as detailed in Table 13. While in ECZTRA 1 and 2, only participants without the use of topical corticosteroids (TCS) were considered in the final analysis (non-responder imputation), in the ECZTRA 3 trial, TCS users were not excluded, possibly explaining the results in ECZTRA 3, which were approximately twice as good (> 4-point improvement of the WI-NRS at week 16: 45% in ECZTRA 3 versus 22% averaged from ECZTRA 1 and 2).

For lebrikizumab, another IL-13 inhibitor, a ≥4-point WI-NRS improvement in 43% of patients at week 16 was reported in the ADvocate 1 and ADvocate 2 trials (Silverberg, Guttman-Yassky et al. 2023). The ADhere trial, which included concomitant TCS, showed even better results (Simpson, Gooderham et al. 2023). Apart from methodological differences in the pivotal trials, a higher binding affinity and therefore more effective blockade of IL-13 signalling pathways involved in pruritus could explain the better antipruritic response reported for lebrikizumab versus tralokinumab when used as a monotherapy (Guttman-Yassky, Blauvelt et al. 2020, Miron, Miller et al. 2022, Silverberg, Guttman-Yassky et al. 2023).

Nemolizumab, an antibody targeting the IL-31 receptor α subunit, blocks IL-31, which is considered a key itch mediator not only in AD but also other itchy skin dermatoses like CPG, bullous pemphigoid, DM and scabies. Nemolizumab has shown very promising results in reducing pruritus in AD patients within a few days and progressively up to week 16 in phase 2B and phase 3 trials (Kabashima, Matsumura et al. 2020, Silverberg, Pinter et al. 2020) ARCADIA 1 and 2 (with concomitant topical therapy) (Silverberg, Wollenberg et al. 2024), as detailed in Table 13.

A recent systematic review on the efficacy and effectiveness of biologics for treating pruritus in AD provides more detailed information including the impact on QOL, safety data and current evidence for other biologics such as cendakinumab and eblasakimab (IL-13 receptor inhibitors), fezakinumab (IL-22 inhibitor), tezepelumab (thymic stromal lymphopoietin [TSLP] inhibitor), etokimab (IL-33 inhibitor), astegolimab (ST2 receptor inhibitor), spesolimab (IL-36 receptor inhibitor), rocatinlimab (OX40 receptor inhibitor) and amlitelimab (OX40 ligand inhibitor) (Hołdrowicz and Woźniacka 2024). The

Table 13. Biologics: Summary table of the itch improvement and clinical improvement reported in studies

Disease	Ref.	YOP	Biologic(s)	Study name	Itch improvement	Clinical improvement
AD	(Simpson, Bieber et al. 2016)	2016	Dupilumab	SOLO 1 and 2	≥ 4-Point improvement in WI-NRS at week 16: 38%*	EASI-75 improvement at week 16: 47%*
AD	(Blauvelt, de Bruin-Weller et al. 2017)	2017	Dupilumab (+TCS)	LIBERTY AD CHRONOS	≥ 4-Point improvement in WI-NRS at week 52: 51%*	EASI-75 improvement at week 52: 78%
AD	(Silverberg, Pinter et al. 2020)	2020	Nemolizumab	N/A	≥ 4-Point improvement in PP-NRS at week 16: approx. 70% (not precisely specified) in 30-mg arm	EASI-75 improvement at week 16: approx. 40% (not precisely specified)
AD	(Simpson, Paller et al. 2020)	2020	Dupilumab	AD ADOL	≥ 4-Point improvement in PP-NRS at week 16: 37%	EASI-75 improvement at week 16: 41.5%
AD	(Kabashima, Matsumura et al. 2020)	2020	Nemolizumab	N/A	Median VAS score at week 16: −43%	Mean percent change in EASI at week 16: −46%
AD	(Wollenberg, Blauvelt et al. 2021)	2021	Tralokinumab	ECZTRA 1 and 2	≥ 4-Point improvement in WI-NRS at week 16: 22%*	EASI-75 improvement at week 16: 29%*
AD	(Silverberg, Toth et al. 2021)	2021	Tralokinumab (+TCS)	ECZTRA 3	≥ 4-Point improvement at week 16: 45%	EASI-75 improvement at week 16: 56%
AD	(Paller, Simpson et al. 2022)	2022	Dupilumab	Liberty AD PRESCHOOL	No subjective itch assessment in this age group	EASI-75 improvement at week 16: 44%
AD	(Simpson, Gooderham et al. 2023)	2023	Lebrikizumab (+ TCS)	ADhere	≥ 4-Point improvement at week 16: 51%	EASI-75 improvement at week 16: 69%
AD	(Silverberg, Guttman-Yassky et al. 2023)	2023	Lebrikizumab	ADVOCATE 1 and 2	≥ 4-Point improvement in WI-NRS at week 16: 43%*	EASI-75 improvement at week 16: 56%*
AD	(Silverberg, Wollenberg et al. 2024)	2024	Nemolizumab	ARCADIA 1,2	≥ 4-Point improvement in PP-NRS at week 16: 42%*	EASI-75 improvement at week 16: 43%*
PN	(Ständer, Yosipovitch et al. 2020)	2020	Nemolizumab	N/A	PP reduced by −5.1 NRS (=62%) at week 12	Improvement by ≥ 75% of PN lesions at week 12: 32%
PN	(Kwatra, Yosipovitch et al. 2023)	2023	Nemolizumab	OLYMPIA 2	≥ 4-Point improvement in WI-NRS at week 16: 56%	IGA 0 or 1 at week 16: 38%
PN-like AD	(Pezzolo, Gambardella et al. 2023)	2023	Tralokinumab	N/A	(Mean itch NRS significantly improved at week 4; no precise numbers provided)	IGA 0 or 1 at week 64(?): 76%
PN	(Yosipovitch, Mollanazar et al. 2023)	2023	Dupilumab	Liberty-PN PRIME and PRIME 2	≥ 4-Point improvement in WI-NRS at week 12: 41%*; at week 24: 59%*	IGA 0 or 1 at week 12: 29%*, at week 24: 46%*
PN	(Kwatra, Yosipovitch et al. 2024)	2024	Dupilumab	Post-hoc analysis LIBERTY-PN PRIME and PRIME 2	≥ 4-Point improvement in WI-NRS at week 24: 59%; OR for clinically meaningful improvement 7.6 compared to placebo	N/A
PN	(Yokozeki, Murota et al. 2024) and (Dermatol 2024)	2024	Nemolizumab (+TCS)	N/A	≥ 4-Point improvement of PP-NRS: 62% (30 mg) and < 57% (60 mg); PP-NRS reduced by 62% (30 mg) and 56% (60 mg) at week 16	Change in number of PN lesions: −68% (30 mg), −60% (60 mg)
PsO	(Griffiths, Reich et al. 2015)	2015	Ixekizumab, etanercept	UNCOVER 2 and 3	≥ 4-Point improvement in WI-NRS at week 12: ixekizumab Q2W 84%*, etanercept 61%*	PASI 90 improvement with ixekizumab Q2W at week 12: 70%*, etanercept 22%*
PsO	(Strober, Sigurgeirsson et al. 2016)	2016	Secukinumab	ERASURE, FIXTURE	Least square mean changes −5.14 (300 mg) at week 12	PASI 90 improvement at week 12: 56%*
PsO	(Kimball, Luger et al. 2018)	2017	Ixekizumab	UNCOVER 1 and 2	Mean improvements in itch severity at week 60 with ixekizumab Q4W −4.9 to −5.0, approx. 80% achieved itch NRS 0 at week 12 and maintained this response to week 60	PASI 90 improvement among patients with itch NRS 0 at week 60: 96%
PsO	(Tang, Vittinghoff et al. 2018)	2018	Guselkumab, adalimumab	VOYAGE 1	≥ 4-Point improvement at week 16: guselkumab 75%; adalimumab 64%	PASI 90 improvement at week 16: guselkumab: 74%; adalimumab 50%
PsO	(Gottlieb, Gordon et al. 2018)	2018	Brodalumab, ustekinumab	AMAGINE 1, 2 and 3	PSI itch responders to ≤ 1 point at week 12: brodalumab 210 mg Q2W: 71%; 140 mg: 61%; ustekinumab 64%	PASI 90 improvement at week 12: 70% (210-mg arm)
PsO	(Blauvelt, Papp et al. 2020)	2020	Ixekizumab, guselkumab	IXORA-R	Complete resolution of itch at week 4: ixekizumab 14%, guselkumab 5% of patients; at week 12: ixekizumab approx. 35%, guselkumab approx. 25%	PASI 90 improvement at week 8: ixekizumab 58%; guselkumab 36%
PsO	(Augustin, Lambert et al. 2020)	2020	Risankizumab, ustekinumab	UltIMMa 1 and 2	PSS Itch item 0/1 at week 16: risankizumab 80%, ustekinumab approx. 65%; at week 52: risankizumab approx. 85%, ustekinumab approx. 62%	PASI 90 improvement at week 16: risankizumab 74%*, ustekinumab 45%*
PsO	(Umezawa, Asahina et al. 2021)	2021	Certolizumab	N/A	WI-NRS=0 at week 16: 400 mg Q2W 38%, at week 52: 51%; 200 mg Q2W: 23% at week 16, 27% at week 32	PASI 90 response rate at week 16: 400 mg Q2W: 82%, at week 52: 88%; 200 mg at week 16: 60%, at week 52: 75%
PsO	(Reich, Papp et al. 2021)	2021	Bimekizumab, ustekinumab	BE VIVID	PSD at week 16: 77% with bimekizumab and 66% with ustekinumab achieved an NRS reduction by ≥ 2.39	PASI 90 improvement at week 16: bimekizumab 85%, ustekinumab 50%
PsO	(Gordon, Foley et al. 2021)	2021	Bimekizumab	BE READY	PSD at week 16: 75% achieved an NRS reduction by ≥ 2.39	PASI 90 improvement at week 16: bimekizumab 91%
PsO	(Costanzo, Llamas-Velasco et al. 2023)	2023	Tildrakizumab	TRIBUTE	Mean absolute change at week 24: of −5.7 NRS	PASI 90 improvement at week 24: 74%
PsO	(Thaçi, Soliman et al. 2021)	2023	Risankizumab vs. fumaric acid	N/A	Least square mean changes −2.5 at week 16, fumaric acid: −1.6	PASI 90 improvement at week 16: 77%; fumaric acid 12%

(Continued)

Table 13. (Continued)

Disease	Ref.	YOP	Biologic(s)	Study name	Itch improvement	Clinical improvement
PsO	N/A	2023	Bimekizumab	BE RADIANT, open label extension	76% Of patients achieved complete resolution of pruritus with PsO (P-SIM item 0 and PASI 100 improvement)	N/A
PsO (difficult-to-treat areas)	(Cacciapuoti, Potestio et al. 2024)	2024	Tildrakizumab	N/A	Mean itch VAS at baseline: 6.1, at week 16: 0.9 itch VAS	PASI 90 response rate at week 16: 45%
Urticaria	(Maurer, Rosén et al. 2013)	2013	Omalizumab	N/A	Reduction of ISS7 (ranging from 0 to 21) at week 12: −9.8 (300 mg) and −8.1 (150 mg)	Weekly number of hives at week 12: −10 (150 mg), −12 (300 mg)
Urticaria	(Maurer, Giménez-Arnau et al. 2019)	2019	Ligelizumab	N/A	At week 12: ligelizumab in all doses (24, 72 and 240 mg) with better reduction of ISS7 compared to omalizumab	Ligelizumab in all doses (24, 72 and 240 mg) with better reduction of weekly UAS7 compared to omalizumab at week 12
Urticaria	(Maurer, Ensina et al. 2024)	2024	Ligelizumab	PEARL 1, 2	Reduction of ISS7 at week 12: −8.5 both in 72-mg and 120-mg ligelizumab group; −8.9 in omalizumab group	Weekly UAS score at week 12: −19.4 in 72-mg and −19.3 in 120-mg ligelizumab group; −20 in omalizumab group
Urticaria	(Maurer, Casale et al. 2024)	2024	Dupilumab	LIBERTY-CSU CUPID	Reduction of ISS7 at week 24: −9*	Reduction of UAS7 at week 24: −17.5*

* = Averaged from two studies.
AD, atopic dermatitis; *EASI*, Eczema Area and Severity Index; *IGA*, Investigator's Global Assessment; *ISS7*, Itch Severity Score over 7 days; *NRS*, numerical rating scale; *OR*, odds ratio; *PASI*, psoriasis area and severity index; *PN*, prurigo nodularis; *PP*, peak pruritus; *PP-NRS*, Peak Pruritus Numerical Rating Scale; *PSD*, patient symptoms diary; *PSI*, psoriasis symptom inventory; *P-SIM*, Psoriasis Symptoms and Impacts Measure; *PsO*, psoriasis; *PSS*, PsO symptom scale; *TCS*, topical corticosteroids; *UAS*, Urticaria Activity Score; *UAS7*, 7-day urticaria activity score; *VAS*, visual analogue scale; *WI-NRS*, Worst Itching Intensity Numeric Rating Scale; *YOP*, year of publication.

effectiveness of biologics to treat pruritus in paediatric AD is summarised in another recent systematic review by Kouwenhoven et al. (Kouwenhoven, van Muijen et al. 2024). In addition, more detailed information on the treatment of AD with biologics can be found in specific AD guidelines (Wollenberg, Barbarot et al. 2018, Wollenberg, Christen-Zäch et al. 2020, Sidbury, Alikhan et al. 2023, Chu, Schneider et al. 2024, Davis, Drucker et al. 2024).

Chronic prurigo

Biologics, particularly dupilumab and nemolizumab, have shown significant efficacy in reducing pruritus in PN. Dupilumab, has been evaluated in several studies, including two phase 3 trials (LIBERTY-PN PRIME and PRIME2), which demonstrated a ≥4-point improvement in the WI-NRS in 41% of patients at week 12 and 59% at week 24, paralleled with a significant improvement of the nodular lesions, skin pain, sleep quality and skin-related QOL compared to baseline (Yosipovitch, Mollanazar et al. 2023, Kwatra, Yosipovitch et al. 2024). A post-hoc analysis has shown that the likelihood of achieving clinically meaningful itch reduction was approximately eight times higher compared to placebo (Kwatra, Yosipovitch et al. 2024). Additionally, a real-life observational study in Chinese patients reported significant improvement in pruritus, clinical presentation and QOL scores with dupilumab as early as after 2 weeks with a progressive effect until week 16 (Fang and Lian 2023).

The phase 3 trial with nemolizumab (OLYMPIA 2) showed that 56% of patients achieved a ≥4-point improvement of the peak pruritus numerical rating scale (PP-NRS) at week 16 compared to 21% in the placebo group. At this study endpoint, approximately one third of all patients were cleared or almost cleared of their skin lesions (Kwatra, Yosipovitch et al. 2023). A recent study from Japan confirmed these favourable findings, showing significant improvement of itch intensity, PN severity, sleep and QOL (Yokozeki, Murota et al. 2024). Nemolizumab was approved by the US Food and Drug Administration (FDA) in August, respectively December, 2024, and is approved in Europe since February 2025 for CPG and AD.

Importantly, these biologics have demonstrated efficacy in PN patients with and without an atopic background. However, it must be taken into consideration that in the LIBERTY-PN PRIME, PRIME 2 and OLYMPIA 2 studies, concomitant use of topical steroids and/or antihistamines was allowed. The safety profiles in these studies were favourable. Common adverse events related to dupilumab included injection-site reactions and conjunctivitis (which may be more prevalent in patients with an atopic background). For nemolizumab, common adverse events included headache and eczema; however, these were typically mild and manageable. Recently, it has been hypothesised that dupilumab could increase the risk of lymphoma in patients with AD; however, causality remains questionable and is not yet clarified.

According to a systematic review of the efficacy of dupilumab in patients with CPG (n=132) or chronic pruritus of unknown origin (CPUO, n=21), the mean time for first improvement was shorter in CPUO patients than in CPG patients (approximately 2 vs. approximately 5 weeks), but at the end of treatment (not specified when), 14% in each group were free of pruritus (Gael, Adam et al. 2022). Interestingly, early improvement was an individual predictor of the future response to dupilumab.

For detailed information on the treatment of CPG and PN, we refer the reader to the IFSI guideline which is currently under revision (Ständer, Pereira et al. 2020).

A summary on other novel biologics for the treatment of PN that are still in the clinical development phase,

such as vixarelimab (oncostatin M receptor [OSMR]-β inhibitor) or barzolvolimab (anti-KIT monoclonal antibody), was recently published by Mueller et al. (Müller, Zeidler et al. 2024).

Psoriasis

Biologics have also shown significant efficacy in reducing pruritus in psoriasis. However, in studies with the TNF-α inhibitors etanercept, infliximab and adalimumab – the first generation of biologics to treat psoriasis – pruritus was not yet a well-established standardised endpoint. In addition, the comparability of the limited study data available is constrained by differences in study designs and the itch assessment tools used. According to a systematic review, only two studies with adalimumab (Revicki, Willian et al. 2007, Revicki, Willian et al. 2008) and one with etanercept (versus secukinumab, FIXTURE study (Langley, Elewski et al. 2014)) qualified for subsequent inclusion in a meta-analysis, in which the mean itch reduction by these TNF-α inhibitors was calculated to be –3.34 points on a 0–10 VAS (Thériné, Brenaut et al. 2018). This effect size was similar to that of JAK inhibitors (tofacitinib and baricitinib, –3.56), greater than that of apremilast (–2.18), but smaller than that of IL-17 inhibitors (ixekizumab and secukinumab, –4.52). Ustekinumab and IL-23 inhibitors were not yet considered in this meta-analysis. Based on this systematic review and meta-analysis, data on the correlation between itch intensity and disease severity (measured using the psoriasis area and severity index [PASI]) are somewhat conflicting. According to pooled data from the AMAGINE 1–2 studies, brodalumab achieved a moderate dose-dependent itch reduction in approximately 60–70% of patients at week 12 (Gottlieb, Gordon et al. 2018). Certolizumab is a TNF-α inhibitor that lacks the Fc region, minimising its transfer across the placenta and making it a potentially safer option for women of childbearing age. In a study from Japan, a dose-dependent itch-relieving effect was observed. By week 16, 38% and by week 52, 51% of participants were free of pruritus at a dose of 200 mg every 2 weeks, indicating that the most benefit occurs in the first 4 months.

For ustekinumab, an IL-12/23 inhibitor, data on its antipruritic potential are available from the head-to-head studies BE VIVID (versus bimekizumab), UltIMMa 1 and 2 (versus risankizumab) and pooled data of the AMAGINE 1–3 studies, in which a significant itch improvement was achieved in two third of patients at week 16 (Gottlieb, Gordon et al. 2018, Reich, Papp et al. 2021) and 12, respectively (and beyond in UltIMMA 1 and 2 (Thaçi, Soliman et al. 2021)). In all of these head-to-head trials, ustekinumab was found to be inferior to its active comparators regarding clinical and itch response.

IL-17 inhibitors are known for their rapid therapeutic effect in psoriasis patients, including itch relief. Both ixekizumab (UNCOVER 1, 2 and 3 studies), secukinumab (ERASURE and FIXTURE studies) and bimekizumab (BE VIVID and BE READY studies) induced a significant itch reduction that started within 2 weeks, improved over time and was durable as detailed in Table 13. Comparability of these study data, however, is limited due to different itch assessments and study duration.

The IL-23 inhibitors risankizumab (UltIMMa 1 and 2 studies, versus ustekinumab), guselkumab (VOYAGE 1 study, versus adalimumab) and tildrakizumab (TRIBUTE study) demonstrated significant itch reduction within a few weeks that was durable and superior to the active comparators (including risankizumab versus fumaric acid). In a recent study, tildrakizumab was also shown to significantly reduce pruritus in psoriasis on difficult-to-treat areas (Cacciapuoti, Potestio et al. 2024).

In the IXORA-R head-to-head trial, complete resolution of itch was reported as early as in week 4 in 14% of patients treated with ixekizumab versus 2% with guselkumab. This superior performance of ixekizumab in this regard persisted until the study end at week 12, indicating that IL-17 inhibitors might be particularly favourable if a rapid and effective itch reduction is desired (Blauvelt, Papp et al. 2020).

More information on the comparative effect of biologics on psoriatic itch can be found in several systematic reviews and meta-analyses as well as specific treatment guidelines on psoriasis (Ellis, Flohr et al. 2019, Menter, Strober et al. 2019, Mahil, Ezejimofor et al. 2020, Nast, Smith et al. 2020, Tada, Watanabe et al. 2020, Xu, Gao et al. 2021, Sbidian, Chaimani et al. 2022, Smith, Yiu et al. 2024).

Urticaria

Multiple studies, including the pivotal study published in 2013 (Maurer, Rosén et al. 2013), have demonstrated the efficacy of omalizumab, an anti-IgE monoclonal antibody, in decreasing itch severity scores in H1-antihistamine resistant CSU. In a systematic review and meta-analysis, omalizumab significantly decreased the weekly Itch Severity Score (ISS7) compared to placebo, with a weighted mean difference (WMD) of –3.94 on a 0–21 range (Jia and He 2020). Significant itch reduction was reported across different doses, including 75 mg, 150 mg and 300 mg, with the 300-mg dose being most effective. In a recent network meta-analysis, this dose-dependent effect size of the WMD was confirmed, but no antipruritic benefit was found for 75-mg doses compared to placebo (Xu, Yu et al. 2024). In a phase 2b head-to-head trial, ligelizumab, a next-generation high-affinity humanised monoclonal anti-IgE antibody, demonstrated a superior antipruritic effect at doses of 24 mg, 72 mg and 240 mg every 4 weeks compared to omalizumab at 300 mg every 4 weeks at week 12 (Maurer, Giménez-Arnau et al. 2019). However, in the subsequent phase 3 studies, PEARL 1 and 2, ligelizumab failed to demonstrate superiority over omalizumab, leading to the discontinuation of its development for the indication

CSU (Maurer, Ensina et al. 2024). Currently, omalizumab remains the only approved biologic for CSU (with some evidence supporting its off-label use in chronic inducible urticaria). However, novel biologics, such as the anti-TSLP monoclonal antibody tezepelumab, the IL-5 inhibitors benralizumab and mepolizumab, as well as dupilumab, are under investigation (Min and Saini 2024). Recently, a promising phase 3 study with dupilumab (LIBERTY-CSU CUPID study) was published (Maurer, Casale et al. 2024). More information on the treatment of urticaria with biologics can be found in the current international guideline (Zuberbier, Aberer et al. 2018).
Expert recommendation: We recommend treating CP in AD using the IL-4/13 inhibitor dupilumab, the IL-31 inhibitor nemolizumab or IL-13 inhibitors such as tralokinumab and lebrikizumab. We recommend treating CP in CPG using dupilumab or the IL-31 inhibitor nemolizumab. We recommend treating CP in psoriasis with a TNF-α inhibitor, IL-17 inhibitor, IL-23 inhibitor or the IL-12/23 inhibitor ustekinumab. We recommend anti-IgE mAb omalizumab to treat CP in CSU.

6.4.12. Small molecules

Small molecules are another group of modern drugs that have revolutionised the treatment of CP associated with chronic inflammatory skin diseases. The key differences compared to biologics include that they: (a) are low-molecular compounds that can easily penetrate cells and act on intracellular targets, allowing for both oral and topical applications; (b) have a broader spectrum of action by blocking multiple signalling pathways with a single drug; (c) offer a faster onset of action due to rapid absorption; (d) have a shorter duration of action, requiring more frequent redosing; and (e) present a broader range of potential side effects due to lower target specificity (Butala, Castelo-Soccio et al. 2023, Yoon, Kim et al. 2024). In recent years, particularly the JAK inhibitors have gained attention for potentially serious side effects, including major cardiovascular events, venous thromboembolism and non-melanoma skin cancers (Liu, Gao et al. 2023, Tsai, Phipatanakul et al. 2024, Yoon, Kim et al. 2024). However, many of these safety signals stem from studies and registries with non-dermatology patients, in which higher doses were used than approved for inflammatory skin diseases (Yang, Kragstrup et al. 2023, Chu, Schneider et al. 2024, Ingrassia, Maqsood et al. 2024, Ireland, Jansson et al. 2024, Yoon, Kim et al. 2024).

Similar to biologics, most publications on small molecules in the context of CP focus on patients with AD and psoriasis, with fewer studies addressing urticaria, PN and chronic hand eczema (see also **Table 14**). Our focus here is on the antipruritic effects of small molecules. For details on the mode of action, on- and off-label indications, dosing, monitoring and safety information, we refer the reader to current guidelines cited in Sect. 6.4.11.

Atopic dermatitis

For AD, the JAK1 inhibitors abrocitinib and upadacitinib and the JAK 1,2 inhibitor baricitinib are approved. Of these three JAK inhibitors, the highest (dose-dependent) > 4 PP or WI-NRS improvement was reported for upadacitinib (MEASURE UP 1 and 2 studies: 60% at week 16 with 30 mg dose, which is not approved for AD in some European countries) (Guttman-Yassky, Teixeira et al. 2021). However, these data are limited by the fact that the duration of the JADE Mono-2 study investigating abrocitinib was only 12 weeks (Silverberg, Simpson et al. 2020). The antipruritic effect of baricitinib appears somewhat weaker according to the BREEZE AD 1, 2 and 7 (Reich, Kabashima et al. 2020, Simpson, Lacour et al. 2020). Two recent systematic reviews and meta-analyses confirmed that high-dose upadacitinib and abrocitinib are among the most effective treatments for reducing pruritus in AD (Chu, Wong et al. 2023, He, Xie et al. 2024). The antipruritic effect of JAK inhibitors typically has a very rapid onset, often appearing within the first 3 days. While none of the systematically reviewed studies added adverse effects leading to discontinuation or serious adverse events, dose-dependent side effects such as acne (abrocitinib, upadacitinib), herpes zoster (abrocitinib), nausea (abrocitinib), headache (abrocitinib), nasopharyngitis (upadactinib) and elevated blood creatine phosphokinase (upadacitinib, baricitinib) were observed (He, Xie et al. 2024).

In a head-to-head trial (JADE COMPARE study) with the IL-4/13 inhibitor dupilumab, the 200-mg dose of abrocitinib (but not the approved 100-mg dose) demonstrated superior itch response compared to dupilumab at week 2 (Bieber, Simpson et al. 2021). However, neither dose of abrocitinib showed a significant difference from dupilumab in terms of itch improvement or eczema area and severity index (EASI)-75 improvement at week 16. In a second head-to-head study, superiority of abrocitinib 200 mg/day versus dupilumab in terms of itch response at week 2 and EASI-90 response at week 4 was reported (Reich, Thyssen et al. 2022). In the HEADS UP study, upadacitinib 30 mg/day showed a superior itch response compared to dupilumab as early as week 1 and also superior EASI-75 to -100 responses at week 2 and 16 (Blauvelt, Teixeira et al. 2021). In a third head-to-head trial, the JAK inhibitors upadacitinib and abrocitinib were again more effective in the treatment of pruritus and disease severity compared to dupilumab from week 1–16 (Huang, Lu et al. 2024).

In the past 10 years, topical JAK inhibitors have also been investigated in numerous studies, both in paediatric and adult AD patients, as recently summarised in a systematic review (Sadeghi and Mohandesi 2023). While in Europe none of these topicals is yet approved, the JAK 1/2 inhibitor ruxolitinib is approved in the USA in patients aged >12 years and the pan-JAK inhibitor delgo-

citinib in Japan and South Korea for the age of > 2 years. In the TRuE-AD 1 and 2 studies (Papp, Szepietowski et al. 2021), treatment with ruxolitinib 1.5% cream achieved a > 4-point improvement in WI-NRS and an EASI-75 response by week 8, which were even higher than some of the responses reported at weeks 12–16 in studies with oral JAK inhibitors (see Table 14). The long-term effectiveness and good tolerability of topical ruxolitinib were demonstrated over a period of 52 weeks (Papp, Szepietowski et al. 2023).

In a phase 3 study from Japan, delgocitinib 0.5% resulted in a mean reduction of day- and night-time pruritus by approximately –1.5 NRS compared to baseline and in an EASI-75 improvement of 26% at week 4.

The phosphodiesterase-4 (PDE4) inhibitors apremilast (oral), crisaborole (topical) and roflumilast (topical) have also been investigated in AD. The development of apremilast for this indication was discontinued due to only modest efficacy (also including dose-dependent itch response) and increased adverse events including cellulitis.

Crisaborol was the first-in-class topical PDE4 inhibitor, approved in the USA and some other countries for the treatment of AD in patients aged > 2 years. This drug has shown an itch improvement within 8 days to < 1 point on a 0- to 3-point scale in 58% of patients (Paller, Tom et al. 2016). However, the magnitude of benefit for this and several other clinical endpoints was later criticised as not being clinically meaningful, especially when considering common local reactions and alternatives such as topical corticosteroids, which offer a much better benefit–cost profile (Ahmed, Solman et al. 2018).

Topical roflumilast 0.15% has reached market maturity and was recently approved in the USA for patients aged >6 years based on the data of the phase 3 studies INTEGUMENT 1 and 2 (Simpson, Eichenfield et al. 2024). In these two studies, both the itch response and the EASI-75 response at week 1, 2 and 4 were significantly better compared to placebo, but comparability with the topical JAK inhibitors is limited by differences in the study design/duration and endpoint reporting.

Other novel topical small molecules being investigated in clinical studies include tapinarof (an aryl hydrocarbon receptor inhibitor), asivatrep (an anti-TRPV1 antagonist) and difamilast (a PDE4 inhibitor) (Freitas, Gooderham et al. 2022, Kleinman, Laborada et al. 2022, Müller, Maintz et al. 2024).

Chronic prurigo (CPG) and chronic pruritus of unknown origin (CPUO)

Small molecules are also being investigated in CPG, but the level of evidence is still very low. Currently, the best evidence is available from a non-randomised phase 2 open-label study with 10 patients with PN and 10 with CPUO treated with abrocitinib 200 mg/day as monotherapy (Kwatra, Bordeaux et al. 2024). At week 12, the proportion of patients achieving a > 4-point PP-NRS improvement was reported in 8/10 PN patients and 6/10 CPUO patients. These data indicate that abrocitinib might be a promising treatment option in both conditions. Several case reports with baricitinib or the pan-JAK inhibitor tofacitinib and one case series with tofacitinib also support this therapeutic antipruritic and anti-inflammatory potential of JAK inhibitors in PN (He, Ji et al. 2021, Peng, Li et al. 2022, Pereira, Zeidler et al. 2022, Yin, Wu et al. 2022, Agrawal, Sardana et al. 2023, Liu, Chu et al. 2023, Sardana, Mathachan et al. 2023); however, RCTs are needed to determine their role in PN and other forms of CP. As recently reviewed, the oral JAK-1 inhibitors povorcitinib and upadacitinib and topical ruxolitinib are currently being investigated in clinical studies with PN patients (Liao, Cornman et al. 2024, Müller, Zeidler et al. 2024, NCT06773403).

Psoriasis

The best studied small molecule in psoriasis is apremilast, whose antipruritic effect was reported in numerous studies such as ESTEEM 1 and 2, ADVANCE and others (Papp, Reich et al. 2015, Paul, Cather et al. 2015, Van Voorhees, Stein Gold et al. 2020, Stein Gold, Papp et al. 2022, Armstrong, Augustin et al. 2024). According to an analysis of an extension phase to 32 weeks (placebo-controlled phase until week 16), approximately 70% of the reduction in pruritus was achieved within the first 2 weeks (Sobell, Foley et al. 2016). By week 32, apremilast also resulted in an approximate 50% decrease in severity of skin discomfort and pain. All these effects resulted in a significant positive impact on the patients' QOL and burden of disease (Sobell, Foley et al. 2016).

In the head-to-head trial PSOETYK 1 and 2, the tyrosine kinase 2 inhibitor deucravacitinib was superior to apremilast in reducing the Psoriasis Symptoms and Signs Diary (PSSD), including itching at week 16 and 24 (Armstrong, Augustin et al. 2024). According to a separate analysis, the corresponding PASI 90 improvement of deucravacitinib at week 16 was 36% (that of apremilast is not reported) (Lebwohl, Warren et al. 2024). In a small study from Japan conducted in a real-world setting, treatment with deucravacitinib resulted in a median reduction of the PP-NRS by –71% at week 2 compared to baseline, indicating rapid itch improvement similar to that observed with other JAK inhibitors in AD (Hagino, Saeki et al. 2024).

The topical PDE4 inhibitor roflumilast was also investigated in psoriasis patients: a >4-point WI-NRS improvement was reported by approximately 55% of patients at week 6 when using dosages of 0.15% or 0.3%, respectively (Lebwohl, Papp et al. 2020). In the DERMIS 1 and 2 studies with 0.3% roflumilast, the >4-point WI-NRS improvement at week 8 was 68%, the PASI 75 improvement 41%.

Table 14. Small Molecules: Summary table of the itch improvement and clinical improvement reported in studies

Disease	YOP	Ref.	Small molecule	Study name	Itch improvement	Clinical improvement
AD	2020	(Silverberg, Simpson et al. 2020)	Abrocitinib	JADE Mono-2	≥ 4-Point improvement in PP-NRS at week 12: 100 mg 45%, 200 mg 55%	EASI-75 improvement at week 12: 100 mg 44%, 200 mg 61%
AD	2020	(Reich, Kabashima et al. 2020)	Baricitinib	BREEZE-AD 7	≥ 4-Point improvement in WI-NRS at week 16: 2 mg 20%, 4 mg 38%	IGA 0–1 at week 16: 2 mg 24%, 4 mg 31%
AD	2020	(Simpson, Lacour et al. 2020)	Baricitinib	BREEZE-AD 1,2	≥ 4-Point improvement in WI-NRS at week 16: 2 mg 14%*, 4 mg 20%*	EASI-75 improvement at week 16: 2 mg 18%, 4 mg 23%*
AD	2021	(Guttman-Yassky, Teixeira et al. 2021)	Upadacitinib	MEASURE-UP 1, 2	≥ 4-Point improvement in WI-NRS at week 16: 15 mg 47%*, 30 mg 60%*	EASI-75 improvement at week 16: 15 mg 62%*, 30 mg 76%*
AD	2021	(Bieber, Simpson et al. 2021)	Abrocitinib, dupilumab	JADE COMPARE	≥ 4-Point improvement in PP-NRS at week 2: abrocitinib 200 mg 49%, 100 mg 32%, dupilumab 26%; (abrocitinib 200 mg but not 100mg superior to dupilumab)	EASI-75 improvement: abrocitinib 200 mg 60%, abrocitinib 100 mg 71%, dupilumab 65% (not significant)
AD	2021	(Blauvelt, Teixeira et al. 2021)	Upadacitinib, dupilumab	HEADS-UP	≥ 4-Point improvement in WI-NRS at week 16: upadacitinib 56% vs. dupilumab 36%	EASI-75 improvement at week 16: upadacitinib 72%, dupilumab 63%
AD	2022	(Shi, Bhutani et al. 2022)	Abrocitinib, dupilumab	JADE EXTEND	≥ 4-Point improvement in WI-NRS at week 12: in dupilumab responders with abrocitinib 100 mg 82%, with 200 mg 90%; in dupilumab non-responders with abrocitinib 100 mg 38%, with 200 mg 77%	EASI-75 improvement at week 12: in dupilumab responders with abrocitinib 100 mg 90%, with 200 mg 93%; in dupilumab non-responders with abrocitinib 100 mg 68%, with 200 mg 80%
AD	2022	(Reich, Thyssen et al. 2022)	Abrocitinib, dupilumab	N/A	≥ 4-Point improvement in PP-NRS at week 2: abrocitinib 200 mg 48%, dupilumab 26%	EASI 90 improvement at week 4: abrocitinib 200 mg 29%, dupilumab 15%
AD	2022	(Guttman-Yassky, Simpson et al. 2023)	Rocatinlimab	N/A	≥ 4-Point improvement in NRS ranging from 37% (150 mg every 4 weeks) to 56% (300 mg every 2 weeks) at week 16	Significant EASI reductions in all rocatinlimab groups, 150 mg or 600 mg every 4 weeks or 300 mg or 600 mg every 2 weeks
AD	2024	(Huang, Lu et al. 2024)	Upadactinib, abrocitinib, dupilumab	N/A	≥ 3-Point WI-NRS improvement at week 1, 4, 8 and 12:upadacitinib > abrocitinib > dupilumab	EASI-75 improvement at week 1, 4, 8 and 12: upadacitinib > abrocitinib > dupilumab
AD	2016	(Paller, Tom et al. 2016)	Crisaborole	AD-301 and 302	Pruritus score ≤ 1 at day 8: 58%*, at day 29: 63%*	Investigator's Static Global Assessment clear or almost clear: 32%*
AD	2021	(Papp, Szepietowski et al. 2021)	Ruxolitinib	TRuE-AD 1, 2	≥ 4-Point improvement in WI-NRS with 1.5% cream at day 2: 11%*, at week 8: 51%*	EASI-75 improvement at week 8: 62%*
AD	2020	(Nakagawa, Nemoto et al. 2020)	Delgocitinib	N/A	Mean change from baseline at week 4 with 0.5% cream: daytime NRS: −1.5, nighttime NRS: −1.4	EASI-75 improvement at week 4: 26%
AD	2024	(Simpson, Eichenfield et al. 2024)	Roflumilast (topical)	INTEGUMENT 1, 2	≥ 4-Point improvement in WI-NRS with 0.15% cream at week 1 approx. 10%*, at week 2 approx. 25%* and at week 4 approx. 30%* Significantly higher compared to placebo, but not precisely specified	EASI-75 improvement at week 4: 43%*
PN, CPUO	2024	(Kwatra, Bordeaux et al. 2024)	Abrocitinib (200 mg/day)	N/A	≥ 4-Point improvement at week 12: 80% of PN and 60% of CPUO patients; weekly PP-NRS reduced by −78% in PN and by −54% in CPUO patients	PN: IGA improvement by −31% at week 12; CPUO: not specified
PSO	2015	(Papp, Reich et al. 2015)	Apremilast	ESTEEM1	Change in mean VAS at week 16: −31 (on a 0–100 VAS)	PASI 90 improvement at week 16: 10%
PSO	2015	(Paul, Cather et al. 2015)	Apremilast	ESTEEM 2	Minimal clinically important difference (> 20% VAS reduction) achieved at week 16: 67.5%	PASI 90 improvement at week 16: approx. 9%
PSO	2020	(Van Voorhees, Stein Gold et al. 2020)	Apremilast	N/A	≥ 4-Point improvement in whole body NRS 45% and scalp itch NRS 47% at week 16	Scalp Physician Global Assessment response ≤1: 43% at week 16
PSO	2020	(Lebwohl, Papp et al. 2020)	Roflumilast (topical)	N/A	≥ 4-Point improvement in WI-NRS at week 6: 53% with 0.3% cream and 57% with 0.15% cream	IGA score clear or almost clear at week 6: 28% with 0.3% group, 23% in 0.15% group
PSO	2021	(Lebwohl, Stein Gold et al. 2021)	Tapinarof (topical)	PSOARING 1, 2	≥ 4-Point improvement in WI-NRS at week 12: 60%*	PASI 90 improvement at week 12: 20%*
PSO	2022	(Lebwohl, Kircik et al. 2022)	Roflumiast (topical)	DERMIS 1, 2	≥ 4-Point improvement in WI-NRS at week 8: 68%*	PASI 75 improvment at week 8: 41%
PSO	2022	(Stein Gold, Papp et al. 2022)	Apremilast	ADVANCE	≥ 4-Point improvement in Whole Body Itch-NRS at week 16: 43%	Scalp Physician Global Assessment response ≤ 1: 44% at week 16
PSO	2024	(Armstrong, Augustin et al. 2024)	Deucravacitinib, apremilast	POETYK PSO1, 2	Itch item Patient Symptoms and Signs scores at week 16: deucravacitinib −3.1*; apremilast −2.4*	PASI 90 response rate at week 16: 36%
PSO	2024	(Hagino, Saeki et al. 2024)	Deucravacitinib	N/A	Median PP-NRS reduction by −71% at week 2	PASI 90 improvement at week 16: 52%
CSU	2022	(Maurer, Berger et al. 2022)	Remibrutinib	N/A	Itch only assessed by UAS7: Improvements in both hives and itching occurred as early as week 1 and were sustained until week 12	
CSU	2023	(Saini, Giménez-Arnau et al., 2023)	Remibrutinib	REMIX 1,2	Reduction of ISS7 at week 12: −9*	Reduction of UAS7 at week 12: 20*
CSU	2023	(Jain, Giménez-Arnau et al. 2024)	Remibrutinib	N/A	Itch only assessed by UAS7: Improvement at week 4: −18% and at week 52: −22; UAS7=0 achieved in 28% at week 4 and 56% at week 52	
CHE	2024	(Bissonnette, Warren et al. 2024)	Delgocitinib	DELTA 1, 2	≥ 4-Point improvement in HESD itch at week 2: 14%, week 4: 31%, at week 8: 43%	IGA-CHE ≤ 1 at week 16: 24%*
CHE	2024	N/A	Delgocitinib	N/A	≥ 4-Point improvement in weekly WI-NRS at week 16: 47%	N/A

* = Averaged from two studies
AD, atopic dermatitis; *CHE*, chronic hand eczema; *CPUO*, chronic pruritus of unknown origin; *CSU*, chronic spontaneous urticaria; *EASI*, Eczema Area and Severity Index; *HESD*, hand eczema symptom diary; *IGA-CHE*, Investigator's Global Assessment for Chronic Hand Eczema; *ISS7*, Itch Severity Score over 7 days; *NRS*, numerical rating scale; *PASI*, Psoriasis Area and Severity Index; *PN*, prurigo nodularis; *PP-NRS*, Peak Pruritus Numerical Rating Scale; *PsO*, psoriasis; *UAS7*, Urticaria Activity Score over 7 days; *VAS*, visual analogue scale; *WI-NRS*, Worst Itching Intensity Numeric Rating Scale; *YOP*, year of publication

Tapinarof, a topical aryl hydrocarbon receptor-modulating agent that modulates the expression of IL-17 and the skin-barrier proteins filaggrin and loricrin, resulted in a >4-point WI-NRS improvement of 60% at week 12, paralleled by a PASI 90 response of 20% in patients with mild to severe plaque psoriasis (PSOARING study 1 and 2) (Lebwohl, Stein Gold et al. 2021).

These examples of roflumilast and tapinarof demonstrate the strong potential of topical small molecules to relieve itch in psoriasis patients. However, head-to-head trials with systemic small molecules are lacking and comparison of study endpoints is strongly limited due to the clearly higher baseline PASI scores of patients in the studies conducted with systemic apremilast and deucravacitinib.

Chronic spontaneous urticaria

Remibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, has shown significant efficacy in reducing itch in patients with CSU inadequately controlled with H2 antihistamines. In a phase 2b dose-finding trial, it demonstrated a rapid onset of action and a substantial reduction in urticaria symptoms (measured by weekly Urticaria Activity Score [UAS7], which also includes itch) that was maintained until week 12 (Maurer, Berger et al. 2022). Furthermore, a long-term extension study confirmed the sustained efficacy of remibrutinib over 52 weeks, with continued improvement in the UAS7 scores and a favourable safety profile (Jain, Giménez-Arnau et al. 2024). In the phase 3 studies REMIX 1 and 2, remibrutinib 25 mg resulted in a mean reduction of the ISS7 (ranging from 0 to 42 according to 0–6 points for 7 days of the week) by –9 score points and of the UAS7 by –20 points at week 12 (Saini, Giménez-Arnau et al. 2023).

Fenebrutinib is another BTK inhibitor that has demonstrated promising efficacy in a phase 2 study in CSU patients (Metz, Sussman et al. 2021).

While the topical pan-JAK inhibitor delgocitinib is approved in Japan and South Korea for AD, it is only approved for chronic hand eczema in some European countries. According to pooled data (AAD 2024 congress poster (Bauer, Schuttelaar et al. 2024)) from the phase 3 studies DELTA 1 and 2, delgocitinib 2% cream achieved a >4-point improvement of the weekly WI-NRS in 14% of patients at week 2 and in 47% of patients at week 16, respectively (Bissonnette, Warren et al. 2024).

Expert recommendation: We recommend treating CP in AD with the JAK inhibitors upadacitinib, abrocitinib or baricitinib. However, we cannot make a recommendation regarding the treatment with topical JAK inhibitors. We suggest the use of abrocitinib in CPG and CPUO, but cannot make a recommendation regarding the other JAK inhibitors for these indications. We recommend treating CP in psoriasis using apremilast or deucravacitinib, but cannot make a recommendation for topical roflumilast or tapinarof.

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 an evidence-based effect on pain, but much less evidence of its antipruritic effects. A recent meta-analysis from 2022 concludes that acupuncture, auricular acupressure and the combination of acupressure injections and massage could improve UP, but further studies are needed (Lu, Chung et al. 2022). The effect of acupuncture on sensory innervation in the skin was investigated in 10 subjects 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 paraesthetica and meralgia paraesthetica) 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 CKD-aP into two groups: 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 CKD-aP 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 of 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).

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 suppressed 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 generalised 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. Among non-pharmacological interventions, musicotherapy might be very helpful (Demirtas, Houssais et al. 2020).

Transcranial neurostimulation by direct current stimulation (tDCS) or magnetic stimulation (TMS) are experimental, non-invasive techniques to modify itch perception by stimulation of itch processing brain structures. However, these techniques have only been investigated in itch studies involving healthy subjects or in anecdotal single cases so far (Zhu, Zhao et al. 2024). Controlled trials are necessary to determine the role of this experimental approach.

While treatment with cold atmospheric plasma (CAP) has been reported to have beneficial effects on disease severity in AD (Kim, Lim et al. 2021, Moon, Yun et al. 2021, Sun, Zhang et al. 2022), data in terms of itch reduction are conflicting with positive (Kim, Lim et al. 2021) versus no effects (Heinlin, Isbary et al. 2013). Anecdotally, vulvar CP was also successfully treated using CAP (Polat, Erni et al. 2021).

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

6.5. Ultraviolet phototherapy

Ultraviolet (UV)-based therapy is well established for treating pruritus and utilises ultraviolet B (UVB; 290–320 nm) and ultraviolet A (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 are based on the release of anti-inflammatory neuropeptides or the inhibition of pro-inflammatory mediators (e.g. IL-1, TNFα) and immune cells as well as antiproliferative and antifibrotic properties (Legat 2018, Legat 2019). These effects make these different UV treatments particularly useful for treating pruritus associated with inflammatory dermatoses (Steinhoff, Cevikbas et al. 2011). In a very recent study, NB-UVB proved to be not inferior to BB-UVB in CP patients after 6 weeks of treatment (Kupsa, Gruber-Wackernagel et al. 2023).

In AD, phototherapy is a common and valid treatment, inhibiting pruritus by reducing the number 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 without 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 bathwater 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). A recent study with 102 patients of CP of various origin showed that both itch intensity and itch-related QOL was significantly reduced after only 4 weeks of phototherapy irrespective of gender and skin phototype (Merkel, Navarini et al. 2024).

UVB laser may be more effective still 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 an 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, Merkel, Navarini et al. 2021). UVB mainly affects epidermal keratinocytes and Langerhans cells due to its limited penetration into the skin. UVA1, in contrast, reaches to the dermis and can therefore affect T lymphocytes, mast cells and dermal dendritic cells, e.g. induce 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 calcitonin gene-related peptide (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 involving pruritus on primarily non-inflamed or normal appearing skin. It has been particularly effective in many cases of CKD-aP (Saltzer and Grove 1975, Gilchrest, Rowe et al. 1977, Mettang 2016). In an open pilot study using NB-UVB 14/20, CKD-aP patients responded well to treatment (Ada, Seckin et al. 2005). In one study, NB-UVB appeared to be effective in the reduction of CKD-aP (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 to 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). Interestingly, a recent study indicated that the response to NB-UVB in CKD-aP patients correlated positively with their increase in serum vitamin D levels (Kee, Jeon et al. 2024).

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 PV, 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 bathwater 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 little or no 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).

Furthermore, in a recent retrospective cohort study, a positive effect of NB-UVB as an add-on treatment in patients with checkpoint inhibitor-induced pruritus was reported (Papageorgiou, Lazaridou et al. 2023).

Expert recommendation: We suggest UVA and UVB (NB-UVB/BB-UVB) phototherapy for PUO, refractory CP in inflammatory skin diseases, cutaneous lymphoma, CPG and selected cases of systemic pruritus (e.g. CKD-aP, cholestatic pruritus and aquagenic pruritus).

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 same general principles of treatment apply. The older patient with CP characteristically presents a mixed clinical picture of itch-inducing and treatment-relevant comorbidities, very commonly physical and cognitive limitations and polypharmacy; 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, diabetes, hepatobiliary disease or malignancies should be addressed as a first step (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. Elderly patients might be particularly in need of a helping hand to ensure optimal topical treatment. 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.

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 should tricyclic antidepressants such as doxepin due to anticholinergic effects, urinary retention, drowsiness, confusion and QT prolongation (Grinnell, Price et al. 2022). To reduce the risk of side effects, dosing of antihistamines must be tailored according to liver and/or renal function. 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). If systemic steroids are opted for, the duration should be as short as possible and accompanied by osteoprotective treatment. 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), but QT prolongation also needs to be monitored. 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 due to potential hepatotoxicity, gastrointestinal symptoms and dizziness. Thalidomide might be a good option for the elderly patient with inflammatory forms of CP (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, care must be taken in the case of increased photosensitivity or phototoxicity caused by multiple drug use (Leslie 2016). Overall, phototherapy such as NB-UVB is a good treatment option, since it can avoid further polypharmacy; however, in patients with a skin cancer history and/or sun damaged skin, this treatment choice might not be suitable. The patient's (im)mobility may be a further factor limiting the suitability of phototherapy in the elderly.

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 and how to treat the underlying disease, including careful selection of the safest treatments available (Stefaniak, Pereira et al. 2022). 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 Cochrane review update, and as confirmed by a European guideline (Chi, Kirtschig et al. 2017), 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, foetal death and low Apgar score (Chi, Wang et al. 2015). However, a recent study showed a significantly increased risk of low birth weight in cases in which 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). A recent European position paper proposed not using fluticasone propionate in pregnant women (as it is the only topical glucocorticosteroid not metabolised by the placenta), giving instead preference to fourth-generation topical GCs (Vestergaard, Wollenberg et al. 2019). Systemic treatments such as systemic GCs, a limited number of antihistamines, UV phototherapy, e.g. UVA, cyclosporine or azathioprine may be necessary in severe and generalised forms of CP in pregnancy (Stefaniak, Pereira et al. 2022). UV phototherapy is a useful alternative treatment for steroid- or antihistamine-refractory pruritus during pregnancy (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); however, in several countries, they are considered safe on the basis that they have already been prescribed for many years. Of the second-generation antihistamines, loratadine and cetirizine are the best studied (Treudler 2010, Golembesky, Cooney et al. 2018). Recent studies showed no increased risk with fexofenadine and desloratadine compared to the above-mentioned second generation antihistamines (Andersson, Poulsen et al. 2020, Andersson, Torp-Pedersen et al. 2020). They can be prescribed after the first trimester in the case of well-considered indications. The National Birth Defects Prevention Study on the use of antihistamines during early pregnancy found no strong evidence to conclude that birth defects are associated with exposure to antihistamines during early pregnancy. However, for neural tube defects, hypoplastic left heart syndrome and tetralogy of Fallot, there is a slight consistency in positive findings with previous studies (Hansen, Desrosiers et al. 2020).

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. Emollients with polidocanol (2–10%), urea (5–10%) and menthol (1%) might have additional itch-relieving effects and can be considered safe (Stefaniak, Pereira et al. 2022). Caution should be shown with systemic therapy due to possible effects on the foetus. This includes drugs like biologics and small molecules. Special attention must be paid to the diagnosis of intrahepatic cholestasis (ICP), which usually occurs in the third trimester: It is particularly important to recognise ICP and to serially determine the serum bile acid concentration as maternal levels > 100 µl/l are associated with an increased risk for preterm birth, neonatal respiratory distress syndrome and intrauterine death.

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 body volume/body surface area ratio and total weight. In addition, the licensed age for any drug must be taken into account. Individualised management is recommended, particularly as study data on CP in children are scarce.

In all cases, general measures are indicated: Avoidance of the specific and non-specific provocation factors is necessary. Such factors include, e.g. inhalant allergens, microbial agents, food allergens such as egg, milk or peanut (Domínguez, Plaza et al. 2020), harsh textiles, irritant chemicals and emotional stress. The use of moisturisers in an attempt to preserve barrier function is always required; they have been shown to even be able to prevent AD in neonates at risk in the first 32 weeks (Horimukai, Morita et al. 2014). Low- (class 1, 2) to medium-strength (class 3) GCs 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 only in children older than 3 months. Topical capsaicin should not be 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, which was demonstrated to be effective in the treatment of AD, showing a significant reduction in the Scoring Atopic Dermatitis (SCORAD) index compared to the vehicle (Berth-Jones, Pollock et al. 2015, Stevens and Edwards 2015), or a 2% topical ointment of crisaborole (PDE4 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 are H1 antihistamines. 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. Severe sleeping disorders caused by pruritus can be a reason for using first generation antihistamines for a limited time period. There is no mechanistic rationale for treating pruritus-related AD with antihistamines (Metz, Wahn et al. 2013, Mollanazar, Smith et al. 2015, Weisshaar 2020, Koumaki, Gregoriou et al. 2023).
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, Zuberbier, Abdul Latiff et al. 2021). Cetirizine, desloratadine, fexofenadine, levocetirizine and loratadine have been studied in children, and their long-term safety has been well established in the paediatric population. Bilastine is licenced for symptomatic relief of urticaria in children aged 6–11 years at a dose of 1 mg/once daily (Papadopoulos and Zuberbier 2019). Rupatadine has been 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 with good clinical evidence (Potter, Mitha et al. 2016, Nieto, Nieto et al. 2021). If antihistamines fail in CSU in the paediatric population nowadays, pruritus and hives are managed with anti-IgE therapy or immunomodulation (Staubach, Peveling-Oberhag et al. 2020).

Second-generation antihistamines (e.g. loratadine, ceterizine) are thought to be safer for use in children and thus may be preferred to first-generation antihistamines (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). In a comparative study of the toxicity profile of second- and first-generation antihistamines, the severity of poisoning from second-generation antihistamines appears to be considerably lower than poisoning caused by mequitazine (Verdu, Blanc-Brisset et al. 2020). The risk of accidental unsupervised ingestion of over-the-counter first-generation antihistamines responsible for anticholinergic effects and, occasionally, death should also be taken into account (Palmer, Reynolds et al. 2020, Wang, Reynolds et al. 2020). Second-generation antihistamines with appropriate dose adjustment are the first-line therapy

for paediatric CP 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). However, longer study follow-up would be necessary to determine the true carcinogenic risk of UV therapy. Scratching habit reversal can have very positive effects on skin inflammation and the course of AD, as shown in a small placebo-controlled study (Norén, Hagströmer et al. 2018). In this study, habit-breaking therapy of scratching behaviour included clenching of fists for 30 s, pinching a fingernail into the itchy skin or pressing instead of scratching. 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 recent years, several targeted therapies, such as etanercept, adalimumab, ustekinumab, secukinumab and ixekizumab for psoriasis as well as dupilumab, tralokinumab and upadacitinib for AD or omalizumab for CSU, were approved in many European countries to treat itchy inflammatory skin diseases in the paediatric and/or adolescent population.

With the ever-growing number of biologics and small molecules in dermatology, this trend is likely to continue.

In summary, the treatment of pruritus in children is primarily focused on treatment of the skin disease, especially AD. Topical GCs, 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. Targeted therapies are becoming more accessible for paediatric patients, and already-approved drugs can be an option in moderate–severe cases of psoriasis, AD and CSU.

6.7. Psychosomatic therapy (relaxation techniques and psychotherapy)

Psychosomatic therapy of CP often aims to break the vicious cycle of itch and scratching by redirecting scratch impulses. In addition, general or itch-specific techniques are used to increase relaxation and improve coping with illness and/or stress. The psychosomatic approach recognises dysfunctional coping behaviour (itch catastrophising) and stress as causes or provocation factors of CP. In addition to causal and symptomatic therapy, behavioural therapy to avoid scratching can be considered, e.g. conscious suppression of scratching behaviour by intense concentration/distraction or alternative scratching techniques such as habit reversal (Rosenbaum and Ayllon 1981). Habit reversal has been shown to be effective in both adults and children (Daunton, Bridgett et al. 2016, Norén, Hagströmer et al. 2018), but findings are either based on small samples (Rosenbaum and Ayllon 1981) or habit reversal techniques were used in the context of multimodal therapies (Ehlers, Stangier et al. 1995).

Adjuvant psychosocial programmes to reduce CP are most effective in AD (Gieler, Kupfer et al. 2000, Staab, von Rueden et al. 2002, Stangier, Ehlers et al. 2004, Staab, Diepgen et al. 2006, Weisshaar, Diepgen et al. 2008, Heratizadeh, Werfel et al. 2017). Such programmes include strategies to break the vicious cycle of itching and scratching, as well as relaxation and (other) stress management techniques and strategies to deal with relapses. According to a Cochrane review, psychological interventions are recommended (Ersser, Cowdell et al. 2014, Singleton, Hodder et al. 2024). Another meta-analysis on the effectiveness of psychological interventions for adults with skin diseases has shown that psychological treatment approaches have medium to large effects on scratching behaviour and itching, but only moderate effects on skin condition and psychological parameters (Lavda, Webb et al. 2012).

Specific educational programs were developed for in- and outpatients with CP (Long, Long et al. 2006, van Os-Medendorp, Ros et al. 2007, Bathe, Matterne et al. 2009, Evers, Duller et al. 2009, Bosecker, Ständer et al. 2011). However, so far, only a few evaluation studies – which have not produced consistent results – are available. In some cases, there were no effects (Bosecker, Ständer et al. 2011), only short-term effects after 3 months (van Os-Medendorp, Ros et al. 2007) or medium-term effects in the 3- and 6-month follow-ups (Evers, Duller et al. 2009).

There are a few new RCTs investigating the effects of psychological online interventions in the treatment of chronic itch. An online-based mindfulness and self-compassion training programme showed significant intervention effects for itch intensity before sleeping, intensity of scratching, itch bothersomeness and psychological variables (e.g. anxiety, depression) for a follow-up of 13 weeks (Kishimoto, Watanabe et al. 2023). Three other RCTs with online cognitive behavioural therapy (CBT) show no effects (Santer, Muller et al. 2022) or only slight effects (Hedman-Lagerlöf, Fust et al. 2021, Zhai, Tang et al. 2023) on itch intensity.

There are only a few, poorly controlled studies including small samples in which the effectiveness of other psychological techniques was investigated. For example, the effectiveness of hypnotherapy should first be shown in RCTs including larger samples with longer follow-up times (Lopes, Teixeira et al. 2020) before it can be recommended as a treatment strategy

to reduce CP. In a recent RCT, five sessions of hypnotherapy reduced itching from 63 to 25 (VAS 0–100) within 8 weeks. This reduction was stable for 26 weeks (VAS = 30). But again, the number of randomised patients was very small (n=6) (Rotter, Teut et al. 2023). Additional approaches related to psychological aspects of CP that have been shown to relieve itch in CP patients include music intervention (Demirtas, Houssais et al. 2020) or visual exposure to antipruritic colours using immersive virtual reality (Mueller, Carruthers et al. 2020, Baschong, Spiess et al. 2021).

Since the effectiveness of psychological interventions for patients with CP has not been fully proven through RCTs as of yet, the use of appropriate programmes or parts of these programmes can be considered in addition to causal and systemic therapy. Although there are no large RCTs on the effectiveness of habit reversal training as well as mindfulness and self-compassion training, there are clear indications that these techniques are suitable to reduce scratching and should thus be used as complementary treatment for managing CP.

Expert recommendation: We recommend standardised patient education programmes. We suggest habit reversal techniques as well as mindfulness and self-compassion training as a complementary treatment for managing CP.

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