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Pathogenesis and Treatment of Pruritus in Cholestasis

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Abstract

Pruritus is an enigmatic, seriously disabling symptom accompanying cholestatic liver diseases and a broad range of other disorders. Most recently, novel itch-specific neuronal pathways, itch mediators and their relevant receptors have been identified. In addition, new antipruritic therapeutic strategies have been developed

and/or are under evaluation. This review highlights recent experimental and clinical findings focusing on the pathogenesis and actual treatment of pruritus in cholestatic liver disease. Evidence-based therapeutic recommendations, including the use of anion exchange resins cholestyramine, colestipol and colesevelam, the microsomal enzyme inducer rifampicin, the opioid receptor antagonists naltrexone and naloxone, and the serotonin reuptake inhibitor sertraline, are provided.

Itch (pruritus) is an unpleasant sensation that provokes the desire to scratch.[1] Pruritus can be caused by numerous diseases. Accordingly, the International Forum for the Study of Itch has proposed the following classification of pruritus:[2] (i) dermatological itch – caused by primary skin disorders; (ii) systemic itch – caused by systemic diseases, tumours, infectious diseases or pregnancy; (iii) neurological itch – provoked by lesions of the peripheral nervous system (PNS) or CNS; (iv) psychogenic itch – associated with psychiatric diseases such as schizophrenia and depression; (v) mixed forms of itch – in cases where several of the above mentioned conditions coexist; (vi) "other forms of itch" – in cases where the origin of pruritus cannot be determined.[2] Approximately one in five patients with generalized pruritus experience a systemic disease. The chronic form of pruritus disables activities of daily life, disrupts sleep and reduces the quality of life (QOL), leading to depression and even suicidal ideation.

In this review, we focus on putative pathomechanisms and currently available treatment strategies of systemic itch caused by cholestatic diseases.

1. Cholestatic Liver Diseases Associated with Pruritus

Pruritus is a common symptom in cholestatic diseases.[3] These disorders are characterized by an impairment of hepatocellular and/or cholangiocellular bile formation and bile flow. Intrahepatic cholestasis may be caused by pure hepatocyte secretory failure, as observed in intrahepatic cholestasis of pregnancy (ICP), certain forms of drug-induced cholestasis, benign recurrent intrahepatic cholestasis, progressive familial intrahepatic cholestasis, and chronic viral hepatitis B and C infections. However, it can also be due to intrahepatic bile duct damage and secondary hepatocyte secretory failure, as observed in primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC) and paediatric cholestatic syndromes such as the Alagille syndrome. Extrahepatic cholestasis may be caused by obstructive tumours of the pancreatic head or enlarged lymph nodes located in the hilar region compressing the bile ducts. PSC, cholangiocellular carcinomas, bile duct adenomas and biliary atresia induce intraductular obstruction (figure 1). Pruritus is more often seen in intrahepatic than extrahepatic cholestasis. Accordingly, pruritus is more often reported in PBC than PSC.[4]

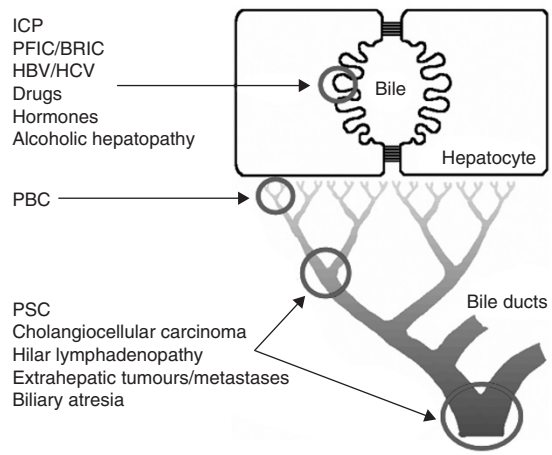

Fig. 1. Common hepatobiliary diseases associated with pruritus. **BRIC** = benign recurrent intrahepatic cholestasis; **HBV** = chronic hepatitis B infection; **HCV** = chronic hepatitis C infection; **ICP** = intrahepatic cholestasis of pregnancy; **PBC** = primary biliary cirrhosis; **PFIC** = progressive familiar intrahepatic cholestasis; **PSC** = primary sclerosing cholangitis.

2. Localization, Fluctuation and Influencing Factors of Cholestatic Pruritus

Patients with cholestatic liver diseases often report most intense itch in the palms and soles, but itch may also be generalized.[5,6] The intensity of pruritus undergoes a circadian rhythm. Patients report highest intensity in the late afternoon, evening and early at night. A circadian rhythm of pruritus intensity was proven when scratching intensity was measured in patients with PBC using piezo-film technology.[5] Circadian fluctuations of substances that attenuate or aggravate itch perception might be responsible for this phenomenon. Interestingly, women with PBC more frequently experience cholestatic pruritus than men with PBC.[7] Pruritus in women exacerbates premenstrually, during hormone replacement therapy and in late pregnancy, suggesting a role for female sex hormones in the generation of itch. Pruritus of different origin has been reported to worsen after intake of certain meals rich in carbohydrates, during sickness, high humidity and in the winter months.[4,5,8-10] However, frequency and intensity of cholestatic pruritus does not correlate with the severity of cholestasis.[4]

In contrast with dermatological itch, specific skin lesions are not observed in patients with cholestatic pruritus, although excoriations and prurigo nodularis[4] may be observed as sequelae of intense scratching activity. Intensity of pruritus varies over a wide range in cholestatic patients. It may be mild and tolerable, but may be aggravated, disturb regular sleep, limit activities of daily life and reduce a patient's QOL, resulting in depression and even suicidal ideation. In cases of intractable refractory pruritus, this symptom may become an indication for liver transplantation even in the absence of liver failure.[3,11-13]

Perception of pruritus, as with pain, differs from one individual to another. Furthermore, intensity of pruritus may be temporarily affected by parenteral, oral or local application of a placebo. Therefore, objective quantification of itch intensity is almost impossible in clinical practice. Use of visual analogue scales (VAS) has been propagated as a form to quantify the sensation itch, but VAS are subject to individual judgement as are other rating forms. Although the sensation itch cannot be measured directly, it leads to scratch movements. These scratch activities are also observed to occur during sleep.[14] They can be quantified with a scratching activity monitoring system (SAMS). This device is based on piezo-electric crystals that are attached to a fingernail and permit registration of every scratch independently of other body movements.[10,15,16] Unfortunately, this sophisticated technique is costly and not generally available. The relevance of adequate quantification of itch intensity is illustrated by contradictory outcomes of clinical trials depending on the methodology used. The serotonin $5HT_3$-receptor antagonist ondansetron was studied in cholestatic patients with itch using either VAS or SAMS as a measure of itch intensity. While VAS was significantly reduced,[17,18] monitoring of scratch activity by use of SAMS did not reveal a beneficial effect of ondansetron in cholestatic pruritus.[19,20] Thus, VAS were suggested to represent an unreliable method of assessing pruritus.[9] However, it might be argued that pruritus therapy first aims to improve patient's well-being and QOL, criteria that are subject to self-evaluation.[21,22]

It is a common experience that intensity of pruritus may be temporarily affected by parenteral, oral or local application of a placebo. This placebo effect might be due to a CNS dopamine release.[23] Hence, randomized, placebo-controlled, double-blinded trials are needed to validate new antipruritic treatment strategies.

3. Pathogenesis of Cholestatic Pruritus

3.1 Interaction between Pain and Itch Signalling

Pain and itch sensations are closely intertwined processes, sharing various signalling pathways. The current, still incomplete, knowledge about the pathophysiology of itch is derived from a number of hypotheses that were proposed during the last century and are briefly summarized in this section.

- The 'intensity theory'. Almost a century ago, itch was regarded as a mild form of pain induced by weak activation of nociceptive nerve fibres.[24] Indeed, both sensations are partly transmitted by unmyelinated C-fibres from the periphery to the spinal cord and CNS. Pain and itch were assumed to share the same communication system to the brain and thus only one of them could talk at a time. The observation that itch perception can be inhibited by pain signals, as induced by scratching or other pain stimuli[25] ('gate control theory'), was in line with this view, although substances such as histamine and the spicula of the fruit mucuna pruriens ('cowhage') induce itch even at high concentrations, whereas weak pain stimuli often do not induce itch.[26,27]
- The 'pattern theory'. Fifty years ago, itch was assumed to be induced by unique spatial and temporal patterns of action potentials.[28,29]
- The 'specificity theory'. In 1997, Schmelz et al.[30] provided evidence for primary afferent neurons specific for histamine in the cutis and subcutis of humans. These itch-specific unmyelinated C-fibres are insensitive to mechanically-induced pain stimuli and transmit their signals from the skin through the dorsal root ganglia to a second neuron in lamina I of the dorsal horn of the spinal cord. The second neuron crosses to the contralateral side and projects via the spinothalamic tract to the ventrocaudal part of the nucleus medialis dorsalis of the thalamus.[31] These observations indicated that itch and pain are transmitted via itch-selective and pain-selective neurons, respectively.[27,32,33] Interestingly, itch signals induced by histamine and cowhage are transmitted by mutually exclusive populations of neurons in the spinal cord,[34] supporting the view that different classes of pruritoceptive nerve fibres exist, as also known for nociceptive neurons. This could explain the different character and treatment response of histamine- and cholestasis-induced pruritus.[35]

Pain and itch perception are intimately intertwined processes. Pain, for example by scratching the skin, represses itch sensations. Antinociception, for example by intrathecally applied μ-opioid receptor agonists or anaesthetics, can induce pruritus.[36] This antagonistic synaptic linkage between nociceptive and pruritoceptive neurons has been postulated to be at the spinal level.[37] Neurons transmitting pruritic stimuli are not spontaneously active in contrast with pain-transmitting neurons.[38] Thus, itch perception seems to be under tonic inhibitory control of mechano-sensitive neurons. This could explain why segmental analgesia induced by spinally or epidurally administered opioids and anaesthetics is often associated with segmental itch.[36] Interestingly, κ-opioid receptor agonists share the antinociceptive qualities of μ-opioid receptor agonists, but also have antipruriceptive properties supposedly by enhancing the inhibitory effect of pain neurons (figure 2).[39]

Multiple sites in the brain, including the primary sensory cortex, supplementary motor area, anterior cingulate cortex and inferior parietal lobe predominantly in the left hemisphere, are activated by histamine-induced itch perception as visualized by positron emission tomography.[40,41] Coactivation of the pre-motor cortical areas may induce the desire to scratch. Interestingly, these itch-activated sites show a wide overlap with those areas being activated by pain sensations.[42] However, a different sensitivity of the posterior cingulate cortex, the posterior insula and, in particular, the thalamus may be responsible for the perceptual difference between itch and pain sensations as indicated by functional MRI.[43] Inhibition of histamine-induced itch by painful cold stimuli revealed an activation of the periaqueductal grey.[41] Thus, the periaqueductal grey being known to modulate noxious stimuli might also be related to central modulation of itch by pain stimuli. Scratching is known to reduce itch sensation as well as noxious pain stimuli.[44] Interestingly, scratching in the absence of itch activated similar sensory and motor areas in the brain as itch does. However, the anterior and posterior cingulate cortices, which are deactivated by scratching, are activated by itch signals.[45]

In summary, itch perception depends on a complex interplay of pruritogens, their receptors, peri-

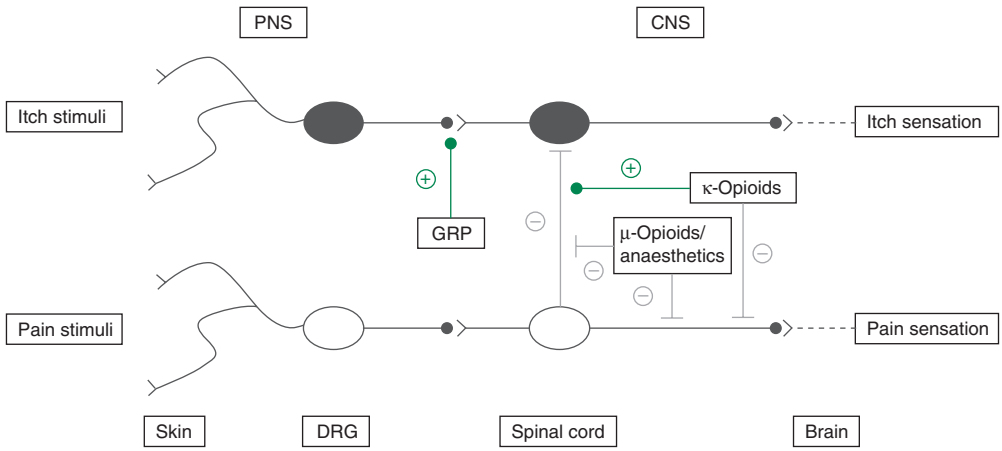

Fig. 2. Simplified schematic representation of pain and itch signalling pathways from the peripheral nervous system (PNS) to the CNS and their interactions (based on an original concept from Schmelz[39]). Anaesthetics, μ- and κ-opioid receptor agonists inhibit pain signalling, whereas spinal modulation of itch signalling is modified oppositionally. Gastrin-releasing peptide (GRP) induces pruritus and is a transmitter of the itch pathway. **DRG** = dorsal root ganglion.

pheral nerve fibres, intraspinal and cerebral neural pathways, as well as cerebral processing in thalamic nuclei and cortical areas that is being increasingly unraveled.[10,46,47]

3.2 Possible Pruritogens in Cholestatic Pruritus

The pathogenesis of pruritus in cholestasis still remains poorly understood and the pruritogens in cholestasis are not yet defined, although bile salts, progesterone metabolites, histamine and endogenous opioids in cholestasis have all been proposed to induce pruritus.[48-50] At present, clinical observations allow the following assumptions: (i) pruritogens are bio-transformed in the liver and intestine because pruritus of cholestasis is improved by the hepatic and intestinal enzyme inducers rifampicin and phenobarbital; (ii) pruritogens are secreted via bile into the intestinal lumen because the intestinal anion exchange resins, cholestyramine, colestipol and colesevelam, which bind many hydrophobic substances in the intestinal lumen, alleviate pruritus in cholestasis; (iii) pruritogens undergo an enterohepatic circulation, because nasobiliary drainage and external biliary diversion induce a dramatic improvement of pruritus in cholestasis; and (iv) the endogenous opioid and serotoninergic systems mediate pruritus in cholestasis because μ-opioid receptor antagonists, κ-opioid receptor agonists and serotonin reuptake inhibitors improve cholestatic pruritus.

3.2.1 Bile Salts

During cholestasis, bile salts (and their protonated form, bile acids), bilirubin and many other cholephiles accumulate in circulation and tissues. The intradermal injection of bile salts induces pruritus in healthy individuals.[51] Anion exchange resins, which bind bile salts inside the intestinal lumen, ameliorate pruritus.[52] However, the most impressive effect is seen in patients with long-lasting intractable pruritus after dilating a major bile duct stenosis or after nasobiliary drainage of bile: within hours, the unpleasant sensation subsides,[53,54] an effect first described a century ago.[55-57] These observations led to the conclusion that cholestatic pruritus may be caused by enhanced concentrations of bile salts in the systemic circulation and peripheral tissues.[58] Additionally, increased levels of total bile salts have been reported in patients experiencing uraemic pruritus caused by chronic renal failure.[59,60] However, several observations question the role of bile salts as a key mediator for cholestatic pruritus:

- Itch is not seen in every patient with cholestatic liver disease and elevated plasma concentrations of bile salts;[61]

- Despite ongoing cholestasis and persistently elevated levels of bile salts, pruritus ameliorates spontaneously in some patients;[4,61]
- No correlation between severity of itch and concentrations of bile salts in circulation and in skin could be proven;[62-64]
- Primary biliary cirrhosis is among the chronic cholestatic liver diseases that are most frequently associated with pruritus, affecting up to 70% of patients.[7] Nevertheless, pruritus is independent of the degree of cholestasis and the stage of disease. It may be observed as the first symptom, long before diagnosis is made, and often diminishes in patients with end-stage disease when bile salts reach their highest levels;
- Anion exchange resins, such as cholestyramine, colestipol and colesevelam, improve itch sensations not only in patients with cholestatic liver disease, but also in patients with chronic renal failure and polycythaemia rubra vera. These diseases are not associated with elevated bile salts in serum and peripheral tissues;[65,66]
- Finally, after nasobiliary drainage, pruritus improved dramatically and disappeared within 24 hours in PBC patients with otherwise therapy-resistant pruritus. In contrast, levels of bile salts in serum initially decreased with a subsequent increase back to baseline values within 7 days when pruritus still subsided. Thus, kinetics of bile salts did not correlate with the intensity of itch in these patients.[54]

Still, it cannot be excluded that certain bile salt metabolites may directly or indirectly contribute to itch perception. However, in summary, the evidence for a key role of bile salts in the induction of pruritus in cholestasis is weak.

3.2.2 Steroids and Steroid Metabolites

Steroids and their metabolites consist of a huge family of substances derived from their precursor molecule cholesterol. After binding to intracellular receptors, various steroids act as transcription factors and regulate gene transcription. In addition, some steroids bind to distinct sites of ligand-gated ion channels and modulate their function.[67,68] These steroids, which influence signalling pathways in the PNS and CNS, are also named neuroactive steroids. Minor structural changes may strongly affect the signalling potency of these neuroactive steroids. For example, pregnanolone (3α-hydroxy-5β-pregnan-20-one) potentiates the chloride current over GABA-A receptors, whereas its 3β-isomer has no effect at all, and its sulfated form strongly inhibits the chloride current.[69] Besides GABA-A receptors, glycine receptors,[70] glutamate receptors, such as NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptors,[71-74] serotonin 5-HT_3 receptors,[75] nicotinic acetylcholine receptors[76] and transient receptor potential vanilloid (TRPV)-1 receptors[77] are sensitive to steroid modulation. Moreover, neuroactive steroids have antinociceptive effects on thermal[78] or capsaicin-induced nociception.[79] As pain perception is intimately intertwined with itch, and both sensations are at least partly elicited via similar receptors, neuroactive steroids might play a role in pruritogenesis.

In line with these observations, pruritus has been reported more often and at higher intensity in women than in men.[7] Similarly, female mice were shown to scratch significantly more than males upon administration of a pruritogen.[80] Levels of steroids and steroid metabolites reach higher concentrations in women than in men. During normal pregnancy, many physiological processes and pathways are altered as a result of dramatically enhanced levels of steroids and steroid metabolites. Some steroids and steroid metabolites are increased more than a 1000-fold, reaching concentrations in the micromolar range.[81] The 'prototype' of pruritus in cholestasis is seen in pregnant women with ICP, which occurs in up to 2% of pregnancies in Europe with a higher incidence in the Northern countries. In ICP, women develop pruritus in the second and more commonly in the third trimester of pregnancy, paralleled by an increase of fasting serum bile acids and serum aminotransferases.[82,83] Within days after delivery, the unpleasant sensation of itch disappears and serum liver tests normalize. Urinary levels of disulfated progesterone metabolites were correlated with intensity of pruritus in a cohort of ICP patients

before and after the start of treatment with ursodeoxycholic acid (UDCA), whereas neither bile salt metabolites nor other steroid metabolites showed a similar correlation.[82,84] Whether disulfated progesterone metabolites either directly or indirectly activate itch-specific neurons or inhibit pain fibres has still to be proven. It may be noticed that reduced dehydroepiandrosterone sulfate levels significantly correlated with fatigue severity in patients with primary biliary cirrhosis,[85] whereas the plasma concentrations of the precursor molecules dehydroepiandrosterone and pregnenolone remained within the levels of controls, further strengthening the potential role of neurosteroids as mediators of CNS symptoms associated with cholestasis. In summary, neuroactive steroids may be regarded as major candidates in mediating pruritus in cholestasis.

3.2.3 Histamine

Histamine is synthesized by decarboxylation of the amino acid histidine and stored in high amounts in the granula of mast cells and basophile granulocytes. Histamine is a potent pruritogen and mediates acute allergic reactions. The release of histamine can be induced by various stimuli, for example binding of IgE antibodies, substance P, vasoactive intestinal peptide and corticotropin releasing hormone.[46,47] Bile salts are capable of releasing histamine from mast cells, albeit at quite high concentrations, in patients with chronic cholestasis[86,87] and in rats with secondary biliary cirrhosis.[88] Furthermore, elevated levels of histamine have been measured in patients with chronic cholestatic liver diseases.[89] However, antihistamines are mostly ineffective in cholestatic pruritus[58] and typical histamine-induced skin lesions, such as flares, erythema and urticaria, are not observed in these patients. Thus, histamine is unlikely to play a major role in the pathogenesis of pruritus caused by cholestatic liver diseases.

3.2.4 Serotonin

Serotonin, which is synthesized from the amino acid tryptophan, has been reported to excite nociceptive nerve fibres.[90,91] As serotonergic receptors modulate the transmission of opioid pain-inhibitory signals in the brain, serotonin might also play a role in itch signalling.[92] Furthermore, serotonin induces itch in humans when it is injected intradermally or applied via iontophoresis.[93,94] Enhanced scratching activity was also observed in mice after injection of serotonin.[95]

Several clinical studies investigated the antipruritic effect of the 5-HT_3-receptor antagonist ondansetron in cholestatic patients with conflicting results.[17-20] Interestingly, the serotonin reuptake inhibitor sertraline was shown to moderately improve pruritus in cholestatic patients.[96,97] It was suggested that this obviously paradoxical effect is due to the dichotomous effects of serotonin on the CNS versus the PNS. Thus, it appears that serotonin is involved in the perception of pruritus in cholestasis to a certain extent, but does not represent a key pruritogen in cholestasis.

3.2.5 Endogenous Opioids

The role of endogenous opioids in the pathogenesis of cholestatic pruritus was first reported in 1979, showing dramatic alleviation of otherwise intractable pruritus in a patient with PBC by the μ-opioid receptor antagonist naloxone.[98] Elevated serum levels of endogenous opioids were observed in the plasma of cholestatic PBC patients[99,100] as well as in rats made cholestatic by bile duct resection.[101,102] However, a correlation between opioid levels and the intensity of itch was never shown.[100] The increased levels of endogenous opioids may be due to enhanced synthesis or reduced elimination.[9,48,103] During cholestasis, messenger RNA levels for preproenkephalin, which codes for Met- and Leu-enkephalins, are elevated in the hepatocytes of bile duct-resected rats,[104] and Met-enkephalin immunoreactivity is enhanced in the periportal areas and proliferating bile ductules of cholestatic rat livers.[105] Thus, hepatocytes and cholangiocytes have been suggested to be the source of elevated endogenous opioids in cholestasis. Endogenous opioids are thought to act in an autocrine-paracrine manner in order to limit cholangiocyte proliferation induced by cholestasis.[106]

Opioids that bind to the μ-opioid receptor induce pruritus in healthy individuals presumably by a central mode of action.[107] Similarly, centrally adminis-

tered opioid agonists induced dose-dependent facial scratching in monkeys.[108] Plasma extracts from four patients with cholestatic pruritus were injected into the medullary dorsal horn of monkeys and led to similar facial scratching, which could be prevented by administering naloxone. In contrast, neither plasma extract from one cholestatic patient without pruritus nor saline induced scratching.[109] In cholestatic rats, opioid receptors were found to be downregulated in different parts of the brain,[110] possibly as a result of increased exposure of endogenous opioids. However, in a cholestatic mouse model, the antinociceptive effect of endogenous opioids (e.g. metenkephalin) was due to local effects at the level of peripheral sensory nerve endings, but not centrally mediated.[111] In summary, endogenous opioids may play an important, but as yet incompletely defined role in pruritus in cholestasis. Their important role is supported by the therapeutic effect of the μ-opioid receptor antagonists, naloxone, naltrexone and nalmefene in patients with cholestatic pruritus.[21,99,112-118]

While μ-opioid receptor antagonists ameliorate pruritus, κ-opioid receptor antagonists have been reported to enhance itch in rats.[119] However, nalfurafine (TRK-820), a new agonist of the κ-opioid receptor, reduced histamine- and substance P-induced itch in mice.[120] In line with these results, nalfurafine improved pruritus in patients with uraemic pruritus.[121] Butorphanol, an antagonist at the μ-opioid receptor and an agonist at the κ-opioid receptor, which is applied as an intranasal spray (1 mg per application), induced relief from itch in a patient with pruritus caused by chronic hepatitis C virus infection.[122] Thus, μ- and κ-opioid receptor agonists may act synergistically in terms of their analgesic properties but inversely in terms of their pruritic properties, and may play a key role in the modulation of pruritus of cholestasis (figure 2).

3.2.6 Gastrin-Releasing Peptide

Recently, Sun and Chen[123] demonstrated a key role of gastrin-releasing peptide (GRP) and its receptor (GRPR) in mediating pruritic stimuli of different origin within the spinal cord. Mice lacking the GRPR scratched significantly less than their wild-type littermates after intradermal application of different itch inducers. Furthermore, scratching could be induced by intrathecal injection of GRP and inhibited by coadministration of a GRPR antagonist. Pain perception induced by thermal, inflammatory or mechanical stimuli was not altered in GRPR mutant mice indicating no relevant role of GRP and its receptor in pain signalling.[123] Thus, GRPR antagonists might be a promising drug for future treatment of different forms of chronic pruritus, but the role of GRP in pruritus of cholestasis remains to be determined.

3.2.7 Endovanilloids

Endovanilloids and their receptors, the so-called TRPV receptors, seem to be involved in mediating pruritic stimuli. TRPV receptors act as non-selective channels for bivalent cations, e.g. calcium and magnesium. The best studied receptor subtype is $TRPV_1$, which is also known as the capsaicin receptor, as capsaicin, the pungent ingredient of red hot chilli peppers, is a $TRPV_1$-receptor agonist. $TRPV_1$ receptor is widely expressed in neurons but also in non-neuronal cell types, including keratinocytes, dendritic cells and dermal mast cells.[124,125] Interestingly, various transmitters and pruritogens activate signalling pathways, which directly or indirectly activate and/or sensitize the $TRPV_1$ receptor. Bradykinin induces activation of the G-protein-coupled bradykinin-2 receptor, which stimulates intracellular phospholipase A_2 and gives rise to 12-lipo-oxygenase metabolites, which, in turn, activate the $TRPV_1$-receptor channel.[126] Similarly, histamine activates $TRPV_1$ receptor in sensory neurons through the phospholipase A_2/lipo-oxygenase pathway.[127] The histamine-induced calcium influx in those neurons can be reduced by capsazepine, a $TRPV_1$-receptor antagonist.[128] Furthermore, mice lacking the $TRPV_1$ receptor scratched significantly less after histamine injection when compared with wild-type mice.[128] Patients with prurigo nodularis show a dramatically increased expression of $TRPV_1$ receptors in epidermal keratinocytes and nerve fibres, which normalized after successful treatment of these pruritic lesions with topical capsaicin.[125] Hence, the vanilloid receptor, $TRPV_1$, can be re-

garded as a molecular integrator of several nociceptive and pruriceptive stimuli, but its role in cholestasis-associated pruritus remains to be determined.

3.2.8 Endocannabinoids

The endocannabinoid system is a further player in the perception and signalling of itch. Endocannabinoids comprise a group of substances that bind to cannabinoid receptors and are mainly structurally related to tetrahydrocannabinol. The cannabinoid subtype 1 (CB_1) receptor is mainly expressed in the CNS, whereas the subtype 2 (CB_2) receptor is found in peripheral tissues. Histamine-induced pruritus is effectively inhibited by cannabinoid agonists.[129] Interestingly, the CB_1 and $TRPV_1$ receptors show a high colocalization in dorsal root ganglia of the rat.[130] Beside neurons, CB_1 and CB_2 receptors are expressed in many different cell types in the skin, including keratinocytes and mast cells.[131] Keratinocytes located around nerve endings in the stratum granulosum of the rat epidermis have been shown to release β-endorphins. This release was induced via a cannabinoid agonist, which binds to CB_2 receptors on β-endorphin expressing keratinocytes. After release, β-endorphins bound to μ-opioid receptors of unmyelinated C-fibres and inhibited nociception in the rats under study.[132] Moreover, endocannabinoids, such as anandamide, have been shown to sensitize $TRPV_1$ receptors demonstrating the complex role of cannabinoids in the modulation of pruritus and pain.[133]

3.2.9 GABA

A potential role of GABA in the pathogenesis of pruritus should be considered. Spinally administered opioids can induce itch, possibly via a disinhibition of the inhibitory transmitters GABA and glycine.[134,135] The GABA agonist propofol, given in a subhypnotic dose of 10 mg, ameliorated spinal morphine-induced pruritus in more than 80% of patients in a prospective, randomized, double-blind, placebo-controlled trial.[134] Similar results were observed in a small, randomized, crossover study of ten patients experiencing pruritus due to different liver diseases. Intravenous infusion of propofol 15 mg was effective in short-term relief of cholestatic pruritus in 85% of patients.[136] The antipruritic effect of propofol is most likely a result of decreased transmission of afferent C-fibres in the dorsal horn of the spinal cord.[107] In line with these findings, the strong GABA-receptor agonist midazolam relieved pruritus in a patient with malignant biliary obstruction.[137] Gabapentin, a potent anticonvulsant drug, was initially synthesized to mimic the chemical structure of GABA, but probably acts via GABA-receptor independent mechanisms. In a randomized, placebo-controlled study, gabapentin failed to improve cholestatic pruritus.[23]

3.2.10 Summary

Cholestasis induces antinociceptive effects in various animal models.[111,138-140] Although pain and itch signals are transmitted via different unmyelinated C-fibres, the signal transduction pathways involved show remarkable similarities. Various receptor ligands are capable of initiating or modulating pain as well as itch perception, albeit not to the same extent. Relevant transmitters of both sensations, such as bradykinin, histamine, serotonin, prostaglandin E_2, endogenous opioids, endocannabinoids and endovanilloids, may contribute to the creation of a milieu in cholestasis that favours both antinociceptive and pruritogenic neuronal activity. Genetic, hormonal and environmental factors may then determine the initiation and extent of pruritus in the individual patient with a cholestatic disorder.

4. Treatment of Cholestatic Pruritus

As the pathogenesis of cholestatic pruritus is still poorly understood, medical and interventional treatment options are limited. Therapeutic efforts should include an adequate therapy of the underlying hepatobiliary disease, which may result in relief of pruritus. Pruritus due to extrahepatic biliary obstruction is effectively treated by endoscopic biliary stenting, transcutaneous or nasobiliary drainage, or surgical biliodigestive anastomoses.[57,58] In contrast, pruritus due to intrahepatic cholestasis may represent an enormous therapeutic challenge in some affected patients. Table I summarizes validated and experimental treatment options for pruritus in cholestatic patients.

Table I. Therapeutic strategies for pruritus in cholestasis[141]

Drug/therapy	Final dose	Recommendation/evidence[a,b]
Efficacy proven in controlled trials		
Ursodeoxycholic acid[c]	10–15 mg/kg/d (PO)[d]	I A – II C[c]
Cholestyramine[c]	4–16 g/d (PO)[e]	I B – IIb C[c]
Rifampicin	300–600 mg/d (PO) 10 mg/kg/d (PO)[d]	I A
Naltrexone	25–50 mg/d (PO)	I A
Naloxone	0.2 μg/kg/min (IV)	I B
Serotonin reuptake inhibitors (e.g. sertraline)	75–100 mg/d (PO)	IIa B
Contradictory efficacy observed in controlled trials		
Ondansetron	4–24 mg/d (PO) 4–8 mg/d (IV)	II A
Efficacy shown in case series or case reports		
Propofol	10–15mg (IV bolus) 1 mg/kg/h (IV)	IIa B
Lidocaine	100 mg/d (IV)	IIa B
Dronabinol	15 mg/d (PO)	IIb C
Butorphanol	1–2 mg/d (intranasal)	IIb C
Phenobarbital	2–5 mg/kg/d (PO)	IIb B
Phototherapy (UVA, UVB)		IIb C
Bright light therapy reflected towards the eyes	10 000 lux 60–120 min/d	IIb C
Plasmapheresis, extracorporeal albumin dialysis (e.g. MARS), plasma separation, anion absorption, nasobiliary drainage, biliary diversion		IIa C
Liver transplantation		I C

a Recommendation grades: I = condition for which there is evidence and/or general agreement that a treatment is beneficial, useful and effective; II = condition for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a treatment; IIa = weight of evidence is in favour of usefulness/efficacy; IIb = usefulness/efficacy is less well established; III = condition for which there is evidence and/or general agreement that a treatment is not useful/effective and in some cases may be harmful.

b Evidence grades: A = multiple randomized clinical trials or meta-analyses; B = single randomized trial or non-randomized studies; C = only consensus opinion of experts, case studies or standard-of-care opinion.

c Recommendation and evidence grade vary depending on the underlying disease (ICP, PSC, PBC).

d Dosage recommended for children and adults.

e Cholestyramine dosage for children: 240 mg/kg/d. For children below the age of 10 years dosage should not exceed 4 g/d, for children aged over 10 years the maximal dose is 8 g/d.

ICP = intrahepatic cholestasis of pregnancy; **IV** = intravenous; **MARS** = molecular adsorbent recirculating system; **PBC** = primary biliary cirrhosis; **PO** = oral; **PSC** = primary sclerosing cholangitis.

A clinical and methodological overview of randomized, placebo-controlled clinical trials conducted with different drugs to treat pruritus in cholestasis is given in table II.

4.1 Ursodeoxycholic Acid

UDCA constitutes up to 3% of the human bile acid pool. However, upon oral administration, UDCA forms up to 50% of bile acids and thereby renders the bile acid pool more hydrophilic.[154,155] In PBC, the most common chronic cholestatic liver disease, UDCA represents the only approved medical treatment. It improves serum liver tests, including cholestatic markers, delays progression to fibrosis and cirrhosis, diminishes the rate of complications, normalizes life expectancy in early-stage disease and may prolong transplant-free survival in a large cohort of patients with stage I–IV PBC.[156] Because of its anticholestatic effect, UDCA is also administered in other cholestatic disorders, such as

Table II. Randomized controlled clinical trials for the treatment of pruritus in cholestasis

Study (year)	n	Duration of therapy	Dose per day	Comparator	Measurement of pruritus (score)	Result
Cholestyramine						
Ducan[142] (1984)	8	2 wk	8 g	Placebo	0–3[a]	Improvement
Di Padova et al.[143] (1984)	10	4 wk	12 g[b]	Placebo	VAS	Improvement
Kondrackiene et al.[144] (2005)	84	2 wk	8–10 g	UDCA	0–4[c]	UDCA better than cholestyramine[d]
Rifampicin						
Ghent and Carruthers[145] (1988)	9	2 wk	300–450 mg	Placebo	VAS	Improvement
Bachs et al.[146] (1989)	22	2 wk	10 mg/kg	Phenobarbital	0–3[a]	Relief/improvement
Woolf and Reynolds[147] (1990)	12	2 wk	300 mg	Placebo	VAS	No improvement
Podesta et al.[148] (1991)	14	2 wk	600 mg	Placebo	VAS	Relief/improvement
Naloxone						
Summerfield[118] (1980)	20	4 d	2 mg bolus	Placebo	VAS/MME	Improvement
Bergasa[113] (1995)	29	2 × 24 h	0.4 mg bolus, 0.2 μg/kg/min infusion	Placebo	VAS/RSM	Improvement
Naltrexone						
Wolfhagen et al.[21] (1997)	16	4 wk	50 mg	Placebo	VAS	Improvement
Terg et al.[116] (2002)	20	2 wk	50 mg	Placebo	VAS	Improvement
Sertraline						
Mayo et al.[97] (2007)	12	6 wk	75–100 mg	Placebo	VAS/RSM	Improvement
Ondansetron						
Schwörer et al.[18] (1995)	10	24 h	4–8 mg	Placebo	VAS	Relief/improvement
Müller et al.[149] (1998)	18	1 wk	24 mg	Placebo	VAS	Improvement
O'Donohue et al.[19] (2005)	19	5 d	8 mg bolus, 8 mg	Placebo	VAS/RSM	No improvement
Jones et al.[20] (2007)	13	4 wk	24 mg	Placebo	VAS/RSM	No improvement
Gabapentin						
Bergasa et al.[23] (2006)	16	4 wk	300–2400 mg	Placebo	VAS/RSM	Placebo better than gabapentin
SAMe						
Ribalta et al.[150] (1991)	18	20 d	900 mg	Placebo	0–4[c]	No improvement[d]
Roncaglia et al.[151] (2004)	46	3–63 d	1000 mg	UDCA	0–4[c]	Improvement equal to UDCA[d]
Binder et al.[152] (2006)	78	14 d through to delivery	1000 mg	UDCA or SAMe + UDCA	1–10[e]	UDCA alone and SAMe + UDCA better than SAMe alone[d]
UDCA						
Palma et al.[153] (1997)	15	3 wk	1000 mg	Placebo	0–4[c]	UDCA better than placebo[d]

a 0 = no pruritus; 3 = severe/continuous pruritus.

b Microporous cholestyramine.

c 0 = no pruritus; 4 = continuous pruritus during day and night-time.

d All patients were women with intrahepatic cholestasis of pregnancy.

e 1 = isolated episodes of pruritus; 10 = continuous pruritus with impairment of sleep rhythm.

MME = movement metre estimation (registration of nocturnal scratch movements); **RSM** = recording of scratch movements; **SAMe** = S-adenosyl-L-methionine; **UDCA** = ursodeoxycholic acid; **VAS =** visual analogue scale (1–10).

PSC, ICP, cystic fibrosis-associated liver disease and paediatric cholestatic syndromes. Several mechanisms and sites of action of UDCA have been unravelled: UDCA (i) improves the impaired

hepatobiliary secretion by stimulating posttranslational synthesis, targeting and apical insertion of key hepatocellular transporters into their target membrane, and also enhances cholangiocyte secretion; (ii) detoxifies bile; and (iii) exerts anti-apoptotic effects both in hepatocytes and cholangiocytes.[157] UDCA is well tolerated and only exceptionally causes diarrhoea.[158] The effect of UDCA on pruritus has never been specifically addressed by therapeutic trials testing antipruritogenic strategies. In randomized, placebo-controlled trials for treatment of PBC or PSC, UDCA has not been convincingly shown to alleviate pruritus in patients affected by this symptom.[159,160] However, small trials reported antipruritic effects of UDCA in children with cholestatic disorders.[161-163] Furthermore, UDCA is a safe and effective therapy in women with ICP, in whom it improved intensity of pruritus, serum liver tests, time of delivery and birthweight of the neonates.[84,144,153]

4.2 Anion Exchange Resins

Anion exchange resins are non-absorbable, alkaline macromolecules that bind anions and amphipathic substances, including bile salts, in the gut lumen and thus prevent their reuptake in the terminal ileum. Cholestyramine and colestipol represent two resins that have been extensively used to treat cholestatic pruritus. Up to 80% of patients responded completely or partially to this drug after 2 weeks of treatment.[52,142,143,164,165] A starting dose of cholestyramine 4 g once or twice a day is recommended, which can be extended to 4 g four times per day. As pruritogens presumably accumulate in the gallbladder overnight, accumulation of anion exchange resins is recommended as a 4 g dose 1 hour before and after breakfast. Anion exchange resins interfere with the absorption of several drugs, such as UDCA, digoxin, warfarin, propranolol and oral contraceptive hormones, as well as fat-soluble vitamins. Thus, anion exchange resins should be taken at least 4 hours prior to any other medication.[166] Adverse effects include abdominal discomfort, bloating, diarrhoea, hypertrigliceridaemia and, rarely, bleeding after long-term use. Colesevelam, a novel bile acid sequestrant being initially used to treat hypercholesterolaemia, has superior binding affinities for bile acids and other amphiphilic substances than cholestyramine or colestipol, and was reported to have no major gastrointestinal adverse effects.[167] Its effect on pruritus needs to be evaluated in controlled trials.

4.3 Rifampicin

The antibiotic rifampicin has been used for the treatment of tuberculosis for decades. This semisynthetic compound derived from *Amycolatopsis rifamycinica* induces phase I and II enzymes and key membrane transporters in the liver by activation of the nuclear steroid and xenobiotic pregnane X receptor.[168] It induces the expression of phase I biotransformation enzymes, such as cytochrome P450 (CYP) 3A4, CYP2D6 and other members of the microsomal CYP system; phase II biotransformation enzymes, such as bilirubin-conjugating enzyme UDP-glucuronosyl transferase (UGT) 1A1 or sulfotransferase SULT2A1; and phase III export pumps, such as canalicular conjugate export pump MRP2.[169,170] Thus, rifampicin accelerates detoxification and excretion of numerous compounds, such as bilirubin, bile acids, steroids and certain drugs. A possible explanation for the antipruritic effect of rifampicin might be an enhanced metabolism and/or increased secretion of direct or indirect pruritogens. Furthermore, its antimicrobial effect on the intestinal flora might alter intestinal metabolism of pruritogens. However, its antipruritic effect cannot only be due to increased CYP3A4 activity because phenobarbital led to a similar induction of CYP3A4 but was inferior regarding the effect on pruritus.[146]

Rifampicin at doses of 300–600 mg/day[145,146,148] and 10 mg/kg/day[171] were reported to improve pruritus in cholestasis. Rifampicin was also effective in children with chronic cholestasis.[172,173] Recent meta-analyses of prospective, randomized, controlled trials revealed that rifampicin is an effective and safe short-term treatment of pruritus,[174,175] whereas hepatotoxicity has been observed in up to 13% of patients after 3 months by some,[171] but not all cohorts during long-term follow-up of up to

72 months.[145,148,173] Thus, serum transaminase levels should be monitored at regular intervals when rifampicin is prescribed.[176] Patients should be informed that rifampicin changes the colour of urine and tears to an orange-red colour, a benign but sometimes frightening adverse effect.

4.4 Opioid Antagonists

Almost 30 years ago, Bernstein and Swift[98] reported an amelioration of cholestatic pruritus in a patient with PBC by the opioid receptor antagonist naloxone. Several clinical trials have proven the positive effect of opioid receptor antagonists on pruritus in patients with hepatobiliary diseases.[175] Naloxone (given as an intravenous bolus of 0.4 mg followed by continuous infusion of 0.2 μg/kg/min),[112,113] nalmefene (60–120 mg/day orally)[99,115] and naltrexone (25–50 mg/day orally)[21,114,116,117] significantly reduced itch and/or scratching behaviour. Nalmefene is no longer available in most countries. Parenterally administered naloxone should be reserved for emergency treatment. Naltrexone was proven to be more effective than placebo in reducing pruritus as well as in improving fatigue and depression.[21,116] Opioid receptor antagonists are well tolerated during long-term treatment, but severe opiate withdrawal-like reactions during the first days of treatment, possibly as a result of an enhanced opioidergic tone in cholestatic patients, have been reported.[99] Therefore, opioid receptor antagonists should be started at very low doses. Alternatively, treatment could be either initiated with intravenous naloxone at subtherapeutic doses (e.g. 0.002 μg/kg/min), then gradually increased before switching to oral naltrexone[177] or coadministered with clonidine (100 mg three times daily), which can be tapered within 1 week.[99] Pruritus may recur during long-term opioid receptor antagonist therapy possibly as a result of drug-induced upregulation of μ-opioid receptors. This breakthrough phenomenon may be prevented by interrupting treatment for 2 days of the week, for example, on Saturdays and Sundays.[114]

The κ-opioid receptor agonist nalfurafine improved pruritus in patients with uraemic pruritus,[121] and the μ-opioid receptor antagonist and κ-opioid receptor agonist butorphanol (1 mg intranasally) alleviated pruritus in a patient with chronic hepatitis C virus infection.[122] Thus, κ-opioid receptor agonists may become new treatment options for cholestatic pruritus in the near future.

4.5 Serotonin Antagonists and Selective Reuptake Inhibitors

Initial studies using subjective methodology reported that intravenous administration of the 5-HT_3 receptor antagonist ondansetron markedly reduced pruritus within hours in patients experiencing cholestatic liver diseases[17,18] and ICP.[178] Controversial results were reported for oral administration of 5-HT_3 antagonists. Only a minor benefit could be demonstrated in a study using a VAS for evaluation of pruritus intensity,[149] but these results were not confirmed when intensity of pruritus was analysed by objective methodology using SAMS.[19,20] Thus, the effectiveness of 5-HT_3 receptor antagonists for the treatment of pruritus in cholestasis remains questionable. In otherwise intractable pruritus, experimental use of intravenously administered 5-HT_3 receptor antagonists may be justified.

The serotonin reuptake inhibitors sertraline[96,97] and paroxetine[179] have been reported to improve pruritus in cholestasis and advanced cancer stages. It remains unclear whether the apparently paradoxical effect of these antidepressants is due to dichotomous effects of serotonin on the CNS versus the PNS,[96] to downregulation of excitatory 5-HT_3 receptors or to a modification of central opioid receptors.[179]

4.6 Cannabinoids

Cannabis was listed in the US Pharmacopeia from 1850 until 1942. However, as a result of its widespread illegal use, its licensed prescription is nowadays controversial. Various cannabinoids from the cannabis plant are ligands of cannabinoid receptors. Dronabinol is a sesame oil preparation of the semi-synthetic analogue of Δ^9-tetrahydrocannabinol, a psychoactive compound of cannabis sativa (marijuana). In three patients with intractable cholestatic pruritus, dronabinol 5 mg every 8 hours tem-

porarily relieved itch, and improved sleep and depression.[180] Interestingly, chronic pruritus of different origin was attenuated after topical application of the cannabinoid receptor agonist *N*-palmitoylethanolamine.[181] Cannabinoids might increase the threshold for the perception of pruritus via stimulation of cannabinoid/opioid receptor interactions on nerve fibres.[180] However, these preliminary observations require further investigations in randomized, placebo-controlled clinical trials.

4.7 Others

4.7.1 Enzyme Inducers

Phenobarbital is a ligand of the nuclear constitutive androgen receptor and induces isoenzymes of the CYP family similar to rifampicin. In a randomized, controlled, crossover study, phenobarbital attenuated pruritus in cholestasis, but was less effective than rifampicin.[146] Other hepatic enzyme inducers, such as flumecinol[182] and the androgen stanozolol,[183] have been reported to attenuate cholestatic pruritus in small case series. The use of stanozolol is limited by the fact that it worsened cholestasis.

4.7.2 Anaesthetics

Propofol at subhypnotic doses (15 mg intravenously) relieved cholestatic pruritus in ten patients with various liver diseases in a prospective, crossover, placebo-controlled trial.[136] Propofol presumably inhibits afferent C-fibres in the dorsal horn of the spinal cord rather than being antipruritic via sedation.[107]

Lidocaine (100 mg intravenously) alleviated pruritus and fatigue in a small cohort of PBC patients when compared with placebo.[22]

4.7.3 S-Adenosyl-L-Methionine

Several clinical trails tested the efficacy of S-adenosyl-L-methionine (SAMe) in comparison with placebo or UDCA in women with ICP.[150-152] Based on the poor outcome of these trials showing no advantage over UDCA, SAMe cannot be recommended for treatment of pruritus in ICP.

4.7.4 Phototherapy

Phototherapy with UV light (UVA, UVB) on the skin[184,185] was reported to alleviate pruritus in cholestatic patients. Chemical modifications of pruritogens in the skin or altered skin sensitivity to pruritogens have been discussed as potential mechanisms of action. However, randomized controlled trials are lacking.

Bright light therapy towards the eyes (1 hour, twice daily) improved pruritus in individual patients,[186] but has been associated with episodes of mania among other adverse effects and should, therefore, only be applied under controlled conditions.

4.7.5 Extracorporeal Elimination of Pruritogens

A beneficial effect of therapeutic procedures such as plasmapheresis,[187] molecular adsorbent recirculating system therapy,[188,189] plasma separation and anion absorption,[190] partial external diversion of bile,[191] ileal diversion in children,[192] and nasobiliary drainage in children[53] and adults[54] with otherwise uncontrollable pruritus has been reported in case series. The temporary success of these procedures supports the view that putative pruritogens in cholestasis accumulate in plasma and undergo an enterohepatic circulation. However, none of the studies were placebo-controlled and the techniques are invasive, very elaborate and too expensive for routine use. Thus, they should only be considered for otherwise intractable pruritus in patients who have exhausted other options.

4.7.6 Liver Transplantation

A successful liver transplantation cures the underlying disease and pruritus is relieved quickly. In patients in whom severe pruritus is refractory to all treatments discussed in this article, this symptom may become an indication for liver transplantation even in the absence of liver failure.[3,11-13]

5. A Step-By-Step Recommendation for the Treatment of Pruritus in Cholestasis

A step-by-step recommendation for the treatment of pruritus in cholestasis is presented in figure 3.

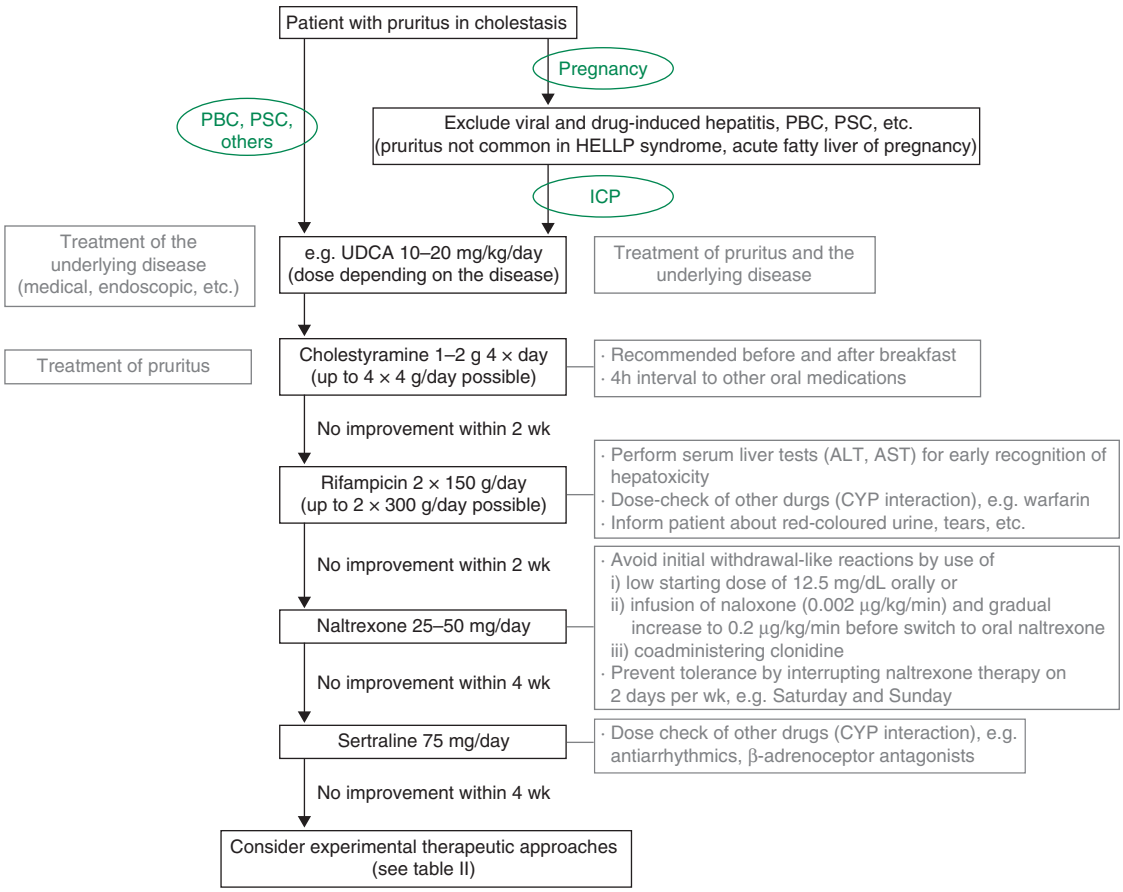

Fig. 3. Step-by-step recommendation for treatment of pruritus in cholestasis. **CYP** = cytochrome P450; **HELLP syndrome** = haemolytic anaemia, elevated liver enzymes and low platelet count; **ICP** = intrahepatic cholestasis of pregnancy; **PBC** = primary biliary cirrhosis; **PSC** = primary sclerosing cholangitis; **UDCA** = ursodeoxycholic acid.

UDCA 10–15 mg/kg/day is regarded as effective first-line treatment of pruritus in ICP and exerts anticholestatic effects in various other cholestatic disorders. Anion exchange resins, such as cholestyramine (4 g before and after breakfast; maximum of 16 g/day), are a first therapeutic step in pruritus of all other forms of intrahepatic cholestasis and extrahepatic forms in which bile flow cannot be restored by invasive procedures. If ineffective, cholestyramine should be stopped after 2 weeks and rifampicin 150 mg should be applied twice daily, which may be increased to a maximum of 600 mg/day. If no response to therapy is achieved within 2 weeks, rifampicin should be discontinued. Naltrexone is recommended as third-line therapy. Withdrawal-like reactions can be avoided by starting with low doses of 12.5 mg/day (or intravenous naloxone infusions, see section 4.4). The antidepressant sertraline 75 mg/day can be administered as fourth-line therapy. Pruritus will improve in most patients in response to these treatment strategies. In patients who do not adequately respond to standard treatment, alternative approaches could be considered as outlined in table I. Coadministration of several drugs at the same time is not recommended because of the risk of drug-drug interactions.

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