

# World Journal of *Gastroenterology*

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## Recent advances in the management of pruritus in chronic liver diseases

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### Abstract

Pruritus is a symptom found in patients with chronic liver diseases, especially cholestatic liver diseases such as primary biliary cholangitis. This symptom impairs

patient quality of life by disturbing sleep and may lead to consideration of liver transplantation. Mechanisms implicated in pruritus have been associated with the peripheral and central nervous systems, leading to the development of various therapeutic options. Little evidence for the efficacy of most of these treatments is currently available, indicating a need for further investigations.

**Key words:** Pruritus; Cholestasis; Autotaxin; Opioid receptor antagonist

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**Core tip:** Pruritus is a symptom influencing the quality of life in patients with chronic liver diseases especially with cholestatic liver diseases. Complex underlying mechanisms have been identified and various therapeutic options developed. More evidence is needed for these treatments, as well as improvements in their tolerability.

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### INTRODUCTION

Pruritus is one of the symptoms encountered in patients with chronic liver diseases, especially in those with cholestatic liver diseases such as primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC)<sup>[1-3]</sup>. Pruritus in patients with cholestasis is characterized by a circadian rhythm, with the highest intensity during the evening and early at night<sup>[4]</sup>. Chronic

pruritus generally tends to increase with warmth and at night<sup>[4,5]</sup>. Women with cholestasis frequently show worsening of pruritus during the progesterone phase of the menstrual cycle, in late pregnancy, and during hormone replacement treatment<sup>[4-6]</sup>. Although pruritus may not be directly associated with the prognosis or outcome of liver diseases, a recent systematic review showed that pruritus has an impact on health-related quality of life in patients with cholestatic liver diseases<sup>[7]</sup>. Pruritus may be an indication for liver transplantation even in the absence of liver failure<sup>[8,9]</sup>. Recently, several mechanisms underlying pruritus, as well as treatment advances have been identified. This review describes recent advances in the management of pruritus in chronic liver diseases.

## MECHANISMS OF PRURITUS IN LIVER DISEASES

Several lines of evidence have suggested mechanisms by which pruritus is induced in cholestatic conditions. First, accumulated bile salts are thought to act as pruritogens<sup>[10]</sup>. Bile salts have been reported to induce degranulation of mast cells *in vitro*, which may contribute to pruritus in cholestatic patients. However the relationship between bile salts and pruritus has not been clarified<sup>[11]</sup>, although some metabolites of bile salts may contribute to pruritus<sup>[12]</sup>. Second, endogenous opioid levels have been reported increased in cholestatic patients<sup>[12,13]</sup>. Activation of  $\mu$ -opioid receptors may cause pruritus by reducing pain signaling, with  $\mu$ -opioid receptor antagonists showing antipruritic effects in patients with chronic cholestasis<sup>[14,15]</sup>. However the correlation between those increased opioid levels and pruritus remains unclear<sup>[12,13]</sup>. Thus, these mechanisms could not fully explain the pathogenesis of pruritus. Furthermore, conditions that may cause skin itching are often found in cirrhotic patients. These include hyperhemodynamic conditions and skin dryness caused by administration of diuretics for hepatic edema<sup>[16]</sup>, complicating the mechanism by which pruritus is induced in cirrhotic patients.

## MECHANISM OF PRURITUS IN THE PERIPHERY

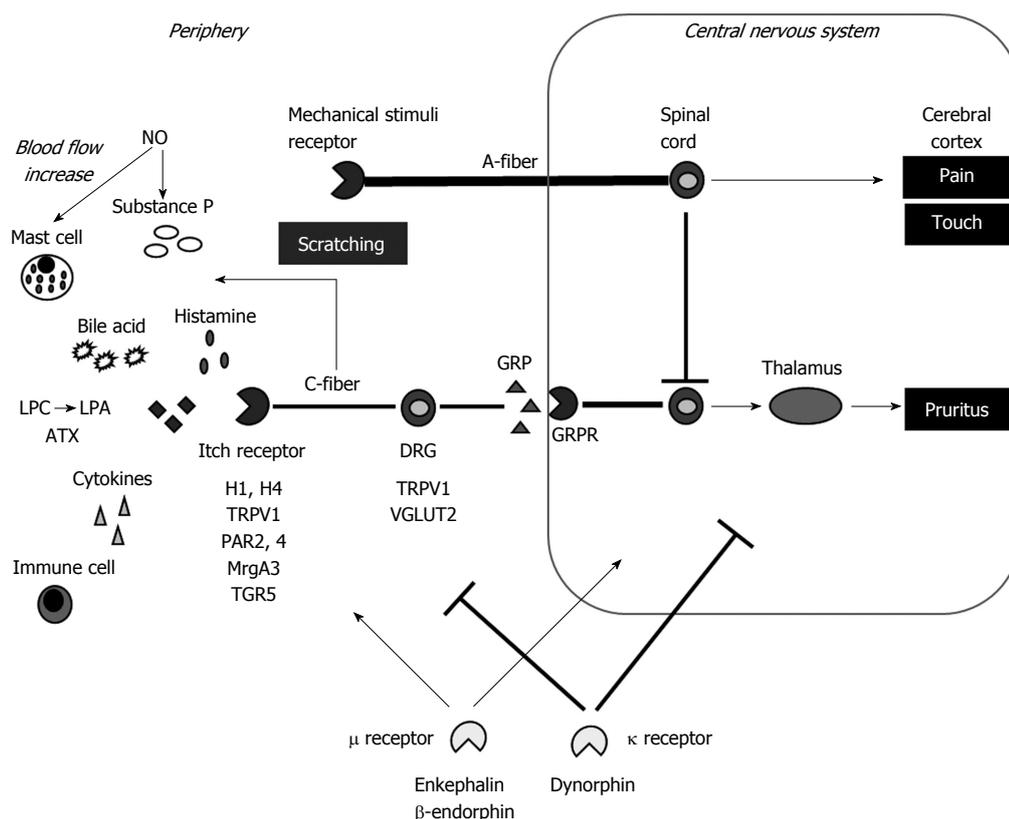
Research in recent decades has clarified mechanisms of pruritus induction in the periphery (Figure 1). The first involves an itch-selective pathway, consisting of slow-conducting C-fibers insensitive to mechanical stimuli, which convey itch signals that are distinct from pain transmission<sup>[17,18]</sup>. Mechanical stimuli such as pain and touch are transmitted through myelinated fast-conducting fibers with larger diameter and competitively inhibit itch-transmission<sup>[19-21]</sup>, thus explaining reason why itching is diminished by scratching<sup>[22]</sup>. Scratching damages the skin barrier, inducing the release of

substance P or calcitonin gene-related peptide, thereby increasing pruritus<sup>[23]</sup>.

Several pruritogens and their receptors specific to itch signaling have been identified. Histamine and the histamine H1 and H4 receptors are considered the main contributors to itch signaling<sup>[24]</sup>. The H1 receptor interacts with phospholipase C $\beta$ 3 (PLC $\beta$ 3)<sup>[25]</sup> and transient receptor potential (TRP) vanilloid receptor subfamily V1 (TRPV1), which constitute a nociceptive ion channel<sup>[26]</sup>. Protease-activated receptors (PAR) 2 and 4 are thought to be involved in itch signaling<sup>[27]</sup>, and PAR2 activation may sensitize TRPV1, thereby contributing to itch<sup>[28,29]</sup>. Serotonin is another pruritogen, which, together with PLC $\beta$ 3, acts on G-protein-coupled receptors (GPCR)<sup>[26]</sup>, such as NK-1, a GPCR shown to play a critical role in serotonin-mediated itch<sup>[30]</sup>. The Mrg subtype A3 (MrgA3), a type of GPCR, is also involved in itch signaling<sup>[31,32]</sup> by interacting with TRPV1<sup>[32]</sup>. Thus, the mechanisms underlying itch signaling is complicated. Other pruritogens may indirectly trigger itch signaling. For example, mast cells are associated with itch not only by releasing histamine but other pruritogens<sup>[33]</sup>. Cytokines produced by immune cells are also involved in itch<sup>[22]</sup>. Keratinocytes (KCs) may also be associated with itching. These cells express the potential itch-associated molecules TRPV3 and 4<sup>[34]</sup>, with TRPV3 expression associated with allergic dermatitis<sup>[35]</sup>. Skin inflammation suggests the involvement of immune cells<sup>[22]</sup>.

Gastrin-releasing peptide (GRP) may act as an itch transmitter<sup>[36]</sup>. GRP is an itch-selective neurotransmitter of dorsal root ganglia (DRG) neurons that activates the GRP receptor (GRPR) on spinal neurons specific to itch not but to pain<sup>[37]</sup>. The vesicular glutamate transporter (VGLUT) 2 was also shown to be involved in itch-selective neurotransmission<sup>[38,39]</sup>.

Lysophosphatidic acid (LPA) has been regarded as a specific target pruritogen/neurotransmitter in patients with cholestasis<sup>[11,12]</sup>. LPA is generated from lysophosphatidylcholine (LPC) by autotaxin (ATX)<sup>[40,41]</sup>. LPA and ATX were shown to be increased in cholestatic patients, suggesting they may be potential therapeutic targets<sup>[11,12,42]</sup>. Serum ATX level was also shown to be increased by the administration of oral contraceptives to healthy females, and was a potential good indicator of intrahepatic cholestasis of pregnancy (ICP)<sup>[43]</sup>. The metabolism of sex hormones is impaired in cirrhotic livers, accompanied by overt feminization<sup>[44]</sup>, thereby partly explaining the mechanism of ATX-induced pruritus in cirrhotic patients. In addition, the G-protein-coupled bile acid receptor 1, TGR5, encoded by *GPBAR1* and expressed on sensory nerves, was recently shown to be involved in pruritus by stimulating the release of neuropeptides in the spinal cord<sup>[45]</sup>. TGR5 was also found to activate the transient receptor potential ankyrin 1 (TRPA1) and to induce pruritus<sup>[46]</sup>. Thus many pruritogens, especially those specific to cholestatic conditions, have been identified.



**Figure 1 Mechanism of itch transmission in cholestatic conditions.** Pruritogens such as histamine, bile acids, bile acid metabolites, LPA and cytokines act on itch receptors. Itch signals are transmitted through C-fibers to the cerebral cortex. The  $\mu$  and  $\kappa$  opioid receptors are expressed in both the central nervous system and the periphery nerve and act to promote and suppress pruritus, respectively. Signals generated by mechanical stimuli compete with itch signals. Scratching induces C-fibers to secrete substance P, and acts as a pruritogen. NO: Nitric oxide; LPC: Lysophosphatidylcholine; ATX: Autotaxin; LPA: Lysophosphatidic acid; GRP: Gastrin-releasing peptide; GRPR: Gastrin-releasing peptide receptor; TRPV1: Transient receptor potential vanilloid receptor subfamily V1; PAR: Protease-activated receptors; MrgA3: Mrg subtype A3; TGR5: G-protein-coupled bile acid receptor 1; VGLUT2: Vesicular glutamate transporter 2.

## MECHANISM OF PRURITUS IN THE CENTRAL NERVOUS SYSTEM

Pruritus also involves the central nervous system (CNS). For example, the most common adverse event of the  $\mu$ -opioid receptor agonist morphine is pruritus<sup>[47,48]</sup>. The  $\mu$ -opioid receptor antagonist naloxone, however, inhibits morphine-induced pruritus<sup>[49]</sup>, and suppresses pruritus in patients with chronic cholestasis<sup>[50]</sup>. Plasma concentrations of the  $\mu$ -opioid receptor agonists methionine enkephalin and  $\beta$ -endorphin were shown to be increased in patients with cirrhosis, as ascites increased due to decreased hepatic elimination<sup>[51,52]</sup>. The liver plays a major role in the elimination of blood-derived opioid peptides<sup>[53]</sup>. These findings suggest that the  $\mu$ -opioid receptor system is involved in pruritus sensations in patients with liver diseases<sup>[54]</sup>. In contrast, the  $\kappa$ -opioid receptor was shown to suppress pruritus. The  $\kappa$ -receptor agonist, nalfurafine (TRK-820) [(E)-N-[17-(cyclopropylmethyl)-4,5 $\alpha$ -epoxy-3,14-dihydroxymorphinan-6 $\beta$ -yl]-3-(furan-3-yl)-N-methylpop-2-enamide monohydrochloride], was shown to suppress anti-histamine-resistant pruritus in a mouse model<sup>[54]</sup>, whereas pruritus was not neutralized by the peripheral administration of the  $\kappa$ -opioid receptor

antagonist nor-binaltorphimine<sup>[54]</sup>. Nalfurafine was also found to suppress pruritus induced by the intracisternal administration of morphine<sup>[55]</sup>. Similar results were observed in a rat model of cholestasis induced by treatment with ethynylestradiol (EE), in which the levels of expression of the  $\kappa$ -receptor agonist dynorphin and nitric oxide (NO) were decreased<sup>[56]</sup>. Nalfurafine showed anti-pruritic activity in this model, an activity partly mediated by NO systems<sup>[56]</sup>. These model indicates that NO is involved in mediating the antipruritic effect of  $\kappa$ -receptor action<sup>[56]</sup>.

NO expression is enhanced in patients with cirrhosis and primary biliary cholangitis, with NO being a main contributor to hyperdynamic circulation in patients with cirrhosis<sup>[16,57]</sup>. NO was shown to enhance substance P-induced scratching in the periphery, whereas a NO synthase inhibitor suppressed this scratching in a dose dependent manner<sup>[58]</sup>. NO induces vasodilatation<sup>[59]</sup>, suggesting it increases peripheral blood flow. Thus the contribution of NO to pruritus remains still controversial and requires further investigation. Furthermore  $\beta$  and  $\kappa$  receptors have been shown to be distributed also in peripheral nerves and contribute to the development of pruritus<sup>[60,61]</sup>. Thus their mechanisms of action are complicated between the periphery and CNS,

especially in patients with chronic liver diseases, making understanding of the pathogenesis of pruritus in these patients difficult and making them refractory to treatment.

## PREVALENCE AND BURDEN OF PRURITUS IN LIVER DISEASES

### **Chronic cholestatic diseases**

Primary biliary cholangitis (PBC), formerly called primary biliary cirrhosis, is a representative chronic cholestatic liver disease manifesting pruritus. Pruritus is found in about 70% of patients with PBC<sup>[2,62]</sup> and precedes the diagnosis of PBC in about 75%<sup>[62]</sup>. Pruritus has been shown to impair quality of life, such as sleep, in patients with PBC<sup>[62,63]</sup>.

Primary sclerosing cholangitis (PSC) is also associated with pruritus during the course of disease progression. In contrast to PBC, most patients with PSC are asymptomatic at the time of diagnosis; therefore the exact prevalence of pruritus in patients with PSC remains unclear<sup>[64]</sup>.

Pruritus in patients with PBC and PSC manifests frequently in the limbs, particularly in the palms and soles<sup>[1,65]</sup>. Multivariate analysis showed that serum alkaline phosphatase activity and Mayo risk score were independent predictors of pruritus in patients with PBC<sup>[66]</sup>. Severe pruritus limits daily life activities and causes fatigue, depression and even suicidal tendencies, becoming an indication for liver transplantation in some patients<sup>[8,67,68]</sup>.

### **Chronic hepatitis and cirrhosis**

Pruritus was observed in four of 49 (8%) patients with chronic hepatitis B and 42 of 210 (20%) with chronic hepatitis C<sup>[69]</sup>. Studies of large cohorts found that the proportion of HCV-infected patients with pruritus ranged from 2.5% of 1060 patients<sup>[70]</sup> to 15% of 1614 patients<sup>[71]</sup>. Pruritus in these patients was not caused by cholestasis<sup>[70]</sup>, whereas liver fibrosis progression was a risk factor contributing to pruritus<sup>[71]</sup>.

### **Other cholestatic conditions**

Pruritus is a defining symptom of intrahepatic cholestasis of pregnancy (ICP), a condition characterized by increases in serum bile acid concentrations and increased rates of adverse fetal outcomes<sup>[72]</sup>. Pruritus in ICP is usually localized to the palms and soles<sup>[73]</sup>. The incidence of ICP was reported to be 1.5%, with increased fetal complications occurring at serum bile acid concentrations > 40<sup>[74]</sup>.

Familial intrahepatic cholestasis, such as benign recurrent intrahepatic cholestasis (BRIC), is an autosomal recessive disorder associated with canalicular transport defects resulting from mutations in *ATP8B1*, *ABCB11* and *ABCB4*. The phenotype is ranging from BRIC to progressive familial intrahepatic cholestasis according to the severity of disease<sup>[75]</sup>.

BRIC is characterized by intermittent jaundice and pruritus, and the clinical symptoms may be severe, last from several weeks to months and usually resolve spontaneously<sup>[75,76]</sup>.

Benign obstructive jaundice has been associated with a lower rate of pruritus than malignant obstruction. For example, pruritus was observed in 16% of patients with benign biliary obstruction such as choledocholithiasis, but in up to 45% of patients with malignant obstruction such as carcinoma of the pancreatic head<sup>[77]</sup>.

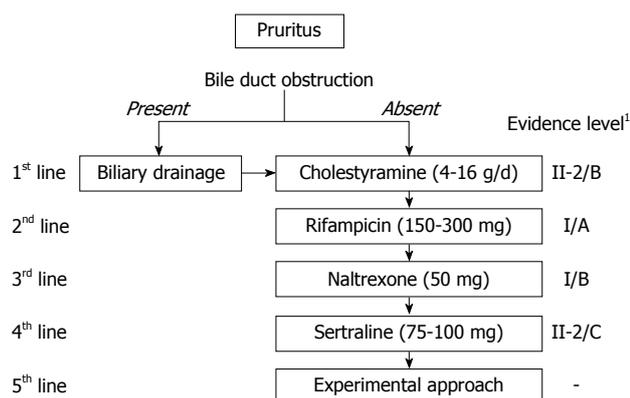
## TREATMENT OF PRURITUS

The guidelines of the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) include criteria for the management of cholestatic pruritus in patients with PBC and PSC<sup>[78,79]</sup>. Recommendations to all patients should include the use of moisturizing and cooling ointments and shortening of the fingernails to avoid secondary skin damage. The principal goals of treatment include<sup>[5]</sup>: (1) removal of pruritogens such as cholestyramine or biliary drainage in the absence of cholestasis; (2) alteration of the metabolism of presumed pruritogens such as rifampicin; (3) modulation of itch signaling such as opioid receptor acting agents; and (4) removal of potential pruritogens by anion absorption, plasmapheresis or extracorporeal albumin dialysis (Figure 2).

Ursodeoxycholic acid (UDCA) is an established drug for the management of PBC and PSC<sup>[80,81]</sup>. Although associated with biological and histological improvements and improving overall survival<sup>[80,81]</sup>, UDCA was ineffective in relieving cholestatic pruritus in both PBC and PSC<sup>[66,82]</sup>. In patients with ICP, however, UDCA not only improved biological parameters such as aspartate aminotransferase and alkaline phosphatase concentrations, but ameliorated pruritus<sup>[74,83]</sup>. UDCA is used for BRIC to stimulate hepatobiliary secretion of bile salts. Antiapoptotic effects of UDCA are also expected to protect hepatocytes in the treatment for BRIC<sup>[75]</sup>.

Cholestyramine, a bile acid resin, has been recommended as the treatment of choice for patients with cholestatic pruritus, as it was shown effective in randomized studies with small numbers of patients (eight and 10, respectively)<sup>[84,85]</sup>. Although generally well-tolerated, cholestyramine has several side effects, including unpleasant taste, fat malabsorption, constipation, anorexia and gastrointestinal discomfort<sup>[86]</sup>.

A meta-analysis of five prospective randomized control trials showed that rifampicin, a pregnane X receptor (PXR) agonist commonly used to treat mycobacterial infection, was effective in treating chronic pruritus<sup>[87]</sup>. Rifampicin was shown to reduce ATX expression *in vitro* by a PXR-dependent mechanism<sup>[42]</sup>. Although safe as short-term treatment of chronic pruritus, rifampicin was associated with hepatotoxicity in up to 13% of patients after treatment



**Figure 2** Therapeutic recommendations for the management of cholestatic pruritus modified from American Association for the Study of Liver Diseases guidelines. <sup>1</sup>Evidence level involves categories of evidence and evidence grading. Categories of evidence include: I, randomized controlled trials; II-1 controlled trials without randomization; II-2, cohort and case-control analytic studies; II-3, multiple time series, dramatic uncontrolled experiments; and III, opinions of respected authorities, descriptive epidemiology. Evidence grading includes A: High quality, indicating that further research is unlikely to change confidence in the estimate of effect; B: Moderate quality, indicating that further research may have an important impact on confidence in the estimate of effect and may change that estimate; and C: Low quality, indicating that further research is very likely to have an important impact on confidence in the estimation of effect and is likely to change that estimate. Any change of estimate is uncertain.

for several weeks or months<sup>[88]</sup>. Adverse effects that may lead to discontinuation of therapy include nausea, loss of appetite, hemolytic anemia, renal failure and thrombocytopenia<sup>[87,89]</sup>. Careful monitoring of blood count and liver function tests is required during administration of rifampicin for cholestatic pruritus, and administration for more than 2 wk is not recommended<sup>[90]</sup>.

Prospective placebo-controlled showed that the  $\mu$ -opioid receptor antagonist naltrexone was effective in treating cholestatic pruritus<sup>[91-94]</sup>. Common side effects of opioid antagonists include opiate withdrawal reactions, particularly during the first days of therapy. Contraindications to naltrexone include acute liver injury and severe liver insufficiency. Opioid antagonists should be avoided in patients with drug addictions and those taking opioid containing medications<sup>[95]</sup>. In Japan, nalfurafine, a  $\kappa$ -opioid receptor agonist, is available for the treatment of pruritus in chronic liver diseases (2.5-5  $\mu$ g/d). Nalfurafine is metabolized predominantly by cytochrome P450<sup>[96]</sup>, but its main metabolite has no pharmacological activity, suggesting its availability and effectiveness for treatment of patients with advanced liver diseases<sup>[97]</sup>. Recently a randomized controlled trial showed the effectiveness of nalfurafine by small dose (2.5 or 5  $\mu$ g/d) for refractory pruritus with chronic liver diseases<sup>[98]</sup>.

Sertraline, a selective serotonin re-uptake inhibitor (SSRI), is a fourth-line therapeutic option for patients with cholestatic pruritus. Sertraline (75-100 mg/d) was well-tolerated and showed moderate anti-pruritic effects in a randomized trial with a small number of

patients<sup>[99]</sup>. Because sertraline is largely metabolized in the liver, careful administration (e.g., lower or less frequent dosing) should be considered in patients with advanced liver diseases. Sertraline should not be administered to patients who treated with monoamine oxidase inhibitors for the previous 14 d or those concurrently taking pimozide, and oral sertraline concentrate should not be administered together with disulfiram<sup>[90]</sup>.

The AASLD and EASL guidelines both recommend that patients who show no improvement on these standard therapies be treated by experimental approaches. Case studies have described methods such as plasmapheresis<sup>[100,101]</sup>, albumin dialysis using a molecular absorbent recirculating system (MARS)<sup>[102-104]</sup>, plasma separation and anion absorption<sup>[105]</sup>, ultraviolet B phototherapy<sup>[106]</sup>, nasobiliary drainage<sup>[107]</sup> and surgical intervention such as partial biliary diversion<sup>[75]</sup>. Little evidence is available for the effectiveness of these approaches, suggesting a need for validation prior to standard use. Furthermore therapeutic options recommended by guidelines lack strong evidence, except for rifampicin as second line-treatment. However, rifampicin cannot be administered for longer than 2 wk. Because pruritus is found in patients with chronic liver diseases, especially cirrhosis, therapeutic modalities tolerable for longer times are needed. A large-scale ( $n = 337$ ), placebo-controlled study showed that nalfurafine was effective and safe in hemodialysis patients with uremic pruritus resistant to conventional treatments<sup>[108]</sup> and that this treatment was tolerable for 52 wk<sup>[109]</sup>. Its effectiveness in treating pruritus in patients with chronic liver diseases was also shown by a randomized controlled study ( $n = 318$ )<sup>[98]</sup>. Its tolerability is under investigation. The effectiveness and tolerability in non-Japanese or non-Asian people are desired.

Recent studies have assessed the association of nuclear receptors with the homeostasis of bile acids, with farnesoid X receptor (FXR) shown to regulate bile acid synthesis<sup>[110,111]</sup>. Obeticholic acid, a FXR agonist, showed significant improvements in biochemical parameters, but increased pruritus rates<sup>[112]</sup>. The incidence and severity of pruritus were reported to be independent of PBC disease stage<sup>[113,114]</sup>, and the mechanism of FXR-induced pruritus remains unknown. The effect of FXR agonist on ATX level should be evaluated.

## CONCLUSION

The mechanism of cholestatic pruritus in chronic liver diseases is complex. The various mechanisms at the periphery and in the central nervous system result complicate determinations of its pathogenesis and treatment strategies. Pruritus occurs frequently in patients with chronic liver diseases, especially those with chronic cholestatic diseases, and impairs patient

quality of life. Current treatments for cholestatic pruritus are inadequate, and additional, more effective therapeutic options are required.

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