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NARRATIVE REVIEW

# Farnesoid X Receptor Agonists: A Promising Therapeutic Strategy for Gastrointestinal Diseases

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**Farnesoid X receptor (FXR) agonists have emerged as a promising therapeutic strategy for the management of various gastrointestinal (GI) diseases, including primary biliary cholangitis, nonalcoholic fatty liver disease, inflammatory bowel disease, alcohol-related liver disease, and primary sclerosing cholangitis. In this review, we discuss the mechanisms of action of FXR agonists, including their metabolic and immunomodulatory effects, and provide an overview of the clinical evidence supporting their use in the treatment of GI diseases. We also highlight the safety, adverse effects, and potential drug interactions associated with FXR agonists. While these agents have demonstrated efficacy in improving liver function, reducing hepatic steatosis, and improving histological endpoints in primary biliary cholangitis and nonalcoholic fatty liver disease, further research is needed to determine their long-term safety and effectiveness in other GI diseases, such as inflammatory bowel disease, alcohol-related liver disease, and primary sclerosing cholangitis. Additionally, the development of next-generation FXR agonists with improved potency and reduced side effects could further enhance their therapeutic potential.**

*Keywords:* FXR Agonists; Liver Disease; Bile Acids; Metabolic Effects; Immunomodulatory Effects

## Introduction

### Overview of FXR Agonists

Farnesoid X receptor (FXR) agonists are a class of drugs that have shown potential for the treatment of several gastrointestinal (GI) diseases. FXRs are nuclear receptors that are predominantly expressed in the liver and intestine, among other tissues such as adipose tissue, vascular endothelium, and pancreas, and are involved in the regulation of bile acid homeostasis, glucose and lipid metabolism, as well as immune responses.[1,2] FXR agonists are synthetic compounds that act by activating FXRs, leading to the regulation of target genes that play important roles in those biological processes. These agents have shown promise in the treatment of GI diseases, including primary biliary cholangitis (PBC) and nonalcoholic fatty liver disease (NAFLD) among others. As the incidence of GI diseases is increasing worldwide, FXR agonists offer a novel therapeutic strategy to manage these conditions.

## Mechanisms of Action of FXR Agonists for GI Diseases

### Metabolic Effects of FXR Agonists in GI Diseases

FXRs play a crucial role in regulating the metabolism of bile acids, lipids, and glucose. In the liver, FXR activation leads to the suppression of bile acid synthesis and the promotion of bile acid excretion, which can reduce the accumulation of toxic bile acids in the liver. Bile acids are the main endogenous activators of FXR as part of a negative feedback loop. This is mainly driven by the interaction between FXR and small heterodimer partner (SHP). When bile acids are present in high concentrations in the hepatocyte, FXR is activated and stimulates the expression of SHP, which then binds to and inhibits the expression of genes involved in bile acid synthesis from cholesterol, such as CYP7A1 and CYP8B1. SHP activation also promotes the conjugation of bile acids with taurine or glycine.[3] Furthermore, FXR activation leads to the modulation of the expression of bile acid transporters in both the hepatocytes and distal ileal enterocytes making it a key player in the enterohepatic circulation of bile acids.[4–8]

FXR also plays a role in lipid metabolism by reducing hepatocyte cholesterol accumulation by inhibition of CYP7A1 and CYP8B1 via SHP and FGF19 activation. It further directly promotes free fatty acid beta oxidation, inhibition of hepatic lipogenesis, reduction of very low-density lipoprotein production, and promotion in triglyceride clearance.[9]

***Abbreviations used in this paper:*** **ALD, alcohol-related liver disease; ALP, alkaline phosphatase; FXR, farnesoid X receptor; GI, gastrointestinal; IBD, inflammatory bowel disease; NAFLD, nonalcoholic fatty liver disease; OCA, obeticholic acid; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; SHP, small heterodimer partner; UDCA, ursodeoxycholic acid.**

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In addition, FXR plays a significant role in glucose metabolism by regulating various metabolic pathways in the liver and intestine. Activation of FXR can improve insulin sensitivity in the liver as well as in peripheral tissues like skeletal muscle and adipose tissue. This is achieved by reducing circulating levels of triglycerides and free fatty acids, which impair insulin signaling and reduce pancreatic insulin secretion, resulting in "lipotoxicity". By attenuating this phenomenon, FXR activation leads to increased glycogen synthesis and reduced gluconeogenesis. FXR activation promotes glycogen synthesis by inducing glycogen synthase kinase 3-alpha expression and represses key enzymes involved in gluconeogenesis, such as phosphoenolpyruvate carboxykinase, fructose-1, 6-bisphosphatase 1, and G6Pase, through a SHP-dependent mechanism.[9]

As such, given the central role FXR plays in bile acid, lipids, and glucose metabolism, it is a promising therapeutic target in cholestatic liver diseases such as PBC and primary sclerosing cholangitis (PSC) as well as metabolic liver diseases, specifically NAFLD.

### *Immunomodulatory Effects of FXR Agonists in GI Diseases*

FXR agonists not only regulate metabolic processes but also exert immunomodulatory effects on cells of the innate immune system. Macrophages and dendritic cells express both GPBAR1 and FXR receptors, while evidence suggests that natural killer T cells only express FXR.[10] Activation of these receptors by bile acids in macrophages promotes a shift toward the anti-inflammatory M2 phenotype, which is associated with an upregulation of interleukin (IL)-10 and a downregulation of the proinflammatory cytokines IL-6 and INF-$\gamma$.[11] In dendritic cells, bile acids down-regulate the production of tumor necrosis factor-$\alpha$ and IL-12, which are key cytokines involved in the activation of Th1 cells and the promotion of inflammatory responses.[10] Bile acids also decrease the expression of osteopontin in natural killer T cells, which plays a crucial role in the development of various autoimmune diseases and inflammation.[12,13] Therefore, FXR agonists may have potential therapeutic applications in the treatment of inflammatory bowel disease (IBD) and other autoimmune disorders, where dysregulated innate immune responses play a crucial role in the pathogenesis of the disease.

The key mechanistic effects of FXR and FXR agonists are summarized in (Figure).

## Clinical Evidence for FXR Agonist Usage in GI Diseases

### *Primary Biliary Cholangitis*

PBC, previously referred to as primary biliary cirrhosis, is a rare liver disease caused by autoimmune factors that lead to inflammation and destruction of small and intermediate bile ducts within the liver. The disease progresses slowly over time and can cause cholestasis, liver fibrosis, and, subsequently, cirrhosis and end-stage liver disease. The symptoms and clinical course of PBC can vary among individuals. The pathogenesis of PBC is complicated and involves multiple factors, including immunological changes that cause damage to bile ducts, as well as the toxic effects of cholestasis and bile acids, which contribute to the loss of bile ducts, hepatopathy, and progressive fibrosis.[14–17]

The mainstay of therapy for PBC is ursodeoxycholic acid (UDCA), which improves liver function and prolongs survival and is supported by the current guidelines.[16,18] However, up to 30%–40% of patients with PBC do not respond to UDCA, and there is a need for alternative therapies.[19,20] The FXR agonist obeticholic acid (OCA) was the first drug approved for use in PBC as a second-line therapy in patients who do not respond to UDCA.[16] In a randomized, double-blind, placebo-controlled phase 3 trial (the PBC OCA International Study of Efficacy trial), OCA was demonstrated to significantly reduce biomarkers associated with adverse clinical outcomes in patients with PBC, including alkaline phosphatase (ALP), bilirubin, aspartate aminotransferase, and alanine aminotransferase, compared to placebo.[21] In this 12-month, double-blind, placebo-controlled phase III trial, 217 patients with PBC were randomly assigned to OCA at 10 mg (the 10-mg group) or 5 mg with adjustment to 10 mg if applicable (the 5–10-mg group) or placebo. Compared to placebo, the primary endpoint of ALP level and total bilirubin decrease was met in 46% and 47% in the 5–10-mg and 10-mg groups, respectively. Pruritus, a common adverse effect, was more commonly reported in the OCA groups (56%–68% vs 38%).[21] Similar effects of OCA were seen in a long-term, randomized, double-blind, placebo-controlled phase 2 study in patients with PBC, which was followed up to 6 years. Patients in the OCA 10 mg and 50 mg groups had significant reductions in ALP compared to the placebo group ($P < .0001$).[22] Additionally, OCA improved gamma-glutamyl transpeptidase, alanine aminotransferase, conjugated bilirubin, and immunoglobulin M, as well as observed biochemical improvements through 6 years of open-label extension treatment.

In an open-label extension study, the efficacy of long-term OCA treatment was assessed in a 5-year follow-up. Results from an interim 3-year analysis found that concentrations of ALP and total and direct bilirubin were significantly reduced compared to baseline, suggesting that OCA improves cholestasis and liver injury in the long term.[23]

The effects of OCA on histological endpoints in patients with PBC were also studied in a POISE substudy. Results from this study showed that OCA was associated with significant reductions in collagen area ratio, collagen fiber density, collagen reticulation index, and fibrosis composite score. Additionally, OCA was associated with improvements in ductular injury, fibrosis, and collagen morphometry features.[24] OCA was also shown to improve hepatic bile acid excretion in patients with PBC. In a double-blind, placebo-controlled study, OCA increased the transport of bile acids from blood to bile, resulting in a reduction in the time that

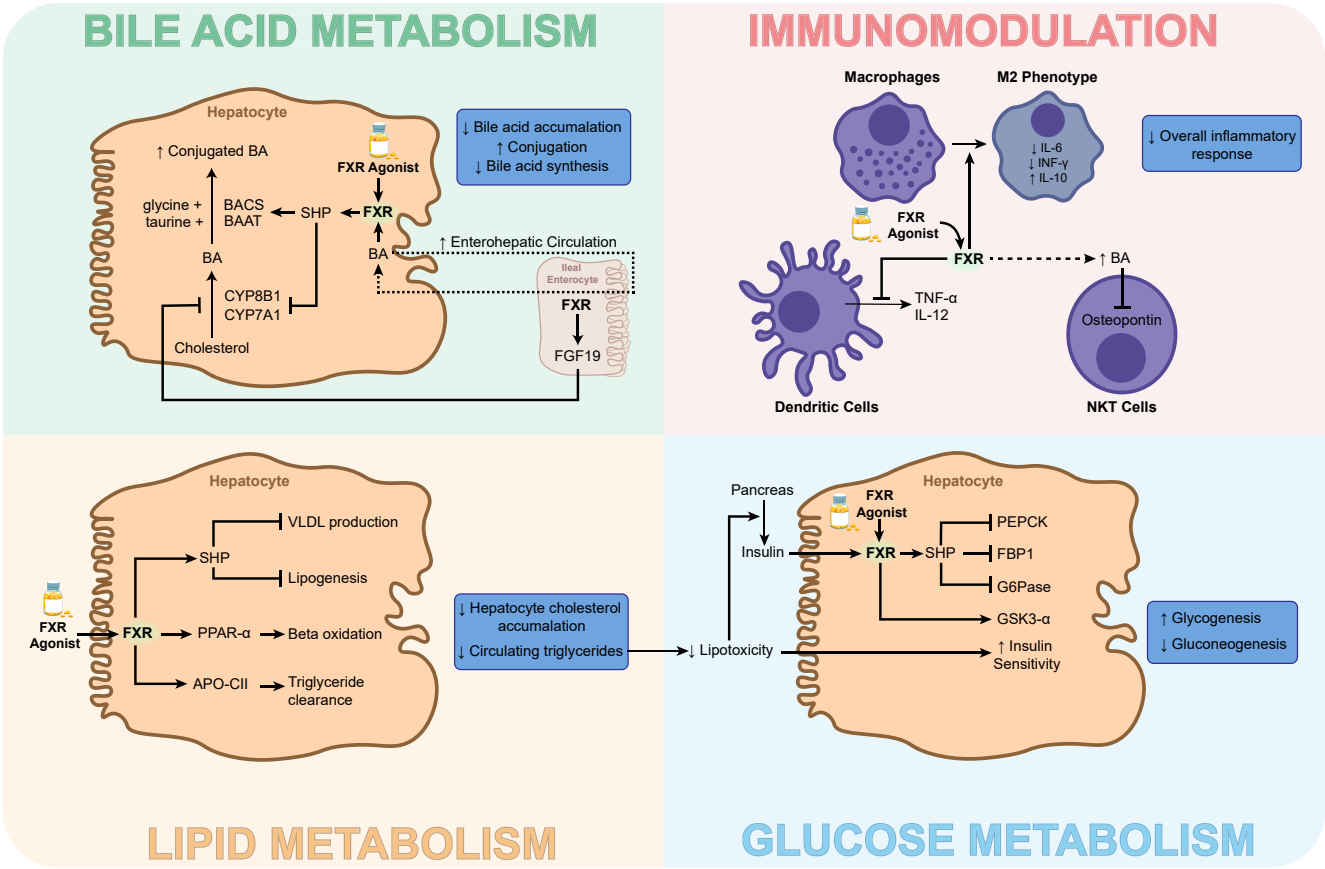


**Figure.** Mechanisms of action of FXR agonists in GI diseases. This figure provides a simplified overview of the mechanisms through which FXR agonists can impact gastrointestinal diseases. The metabolic effects of FXR agonists can be divided into three categories: bile acid metabolism, lipid metabolism, and glucose metabolism. Activation of FXR results in suppression of bile acid synthesis, promotion of bile acid excretion, and reduced toxic bile acid accumulation in the liver. Additionally, FXR activation reduces hepatocyte cholesterol accumulation, promotes free fatty acid beta oxidation, inhibits hepatic lipogenesis, reduces VLDL production, and increases triglyceride clearance. FXR activation also leads to improved insulin sensitivity, reduced circulating levels of triglycerides and free fatty acids, increased glycogen synthesis, and reduced gluconeogenesis. The immunomodulatory effects of FXR agonists can impact macrophages, dendritic cells, NKT cells, and IBD patients. Activation of FXR in macrophages causes a shift toward the anti-inflammatory M2 phenotype, upregulation of IL-10, and downregulation of proinflammatory cytokines IL-6 and INF-$\gamma$. Bile acids can also down-regulate TNF-$\alpha$ and IL-12 in DCs, leading to reduced activation of Th1 cells and decreased inflammatory responses. APO-C11, apolipoprotein C-III; BA, bile acids; BAAT, bile acid-CoA: amino acid N-acyltransferase; BACS, bile acid-CoA synthetase; CYP7A1, Cytochrome P450 Family 7 Subfamily A Member 1; CYP8B1, Cytochrome P450 Family 8 Subfamily B Member 1; FBP1, fructose-1,6-bisphosphatase 1; FGF19, fibroblast growth factor 19; FXR, farnesoid X receptor; G6Pase, glucose-6-phosphatase; GSK3-$\alpha$, glycogen synthase kinase 3-alpha; GI, gastrointestinal; IBD, inflammatory bowel disease; IL, interleukin; INF, interferon; NKT, natural killer T; PEPCK, phosphoenolpyruvate carboxykinase; PPAR-$\alpha$, peroxisome proliferator-activated receptor-alpha; SHP, small heterodimer partner; Th1, T helper 1; TNF, tumor necrosis factor; VLDL, very low-density lipoprotein.

potentially toxic bile acids stayed in the liver by approximately one-third.[25] Finally, OCA was found to reduce and stabilize bilirubin in patients with elevated baseline direct bilirubin levels.[26]

Taken together, these studies suggest that OCA has diverse beneficial effects in reducing cholestasis, improving histological endpoints, and improving hepatic bile acid excretion in patients with PBC (Table).

OCA was first approved in 2016 by the US Food and Drug Administration for use in patients with PBC.[34] The current guidelines from the American Association for the Study of Liver Diseases recommend the use of OCA in patients who are inadequate responders to UDCA.[16] However, it's important to note that OCA has been associated with certain risks. In patients with advanced cirrhosis, OCA has been linked to a worsening of the disease and even death. This is likely due to the drug's effects on bile acid transport, which can potentially exacerbate cholestasis in these patients. Furthermore, high doses of OCA have been linked to an increased risk of serious adverse effects, including severe pruritus and potential hepatotoxicity. Therefore, careful dose titration

**Table.** Summary of FXR Agonists Usage in GI Diseases

| Disease | Agent | Daily dose | Effects | Trials | Citations |
|---|---|---|---|---|---|
| PBC | OCA | 5–10 mg | Reduces biomarkers, improves cholestasis, liver injury, histological endpoints, and hepatic bile acid excretion | POISE, POISE substudy, 12-mo double-blind trial | 21–24,26 |
| NAFLD | OCA | Not specified | Improves insulin sensitivity, liver inflammation, fibrosis, steatohepatitis activity, and histologic activity | FLINT, REGENERATE | 27,28 |
| | Cilofexor | Not specified | Reduces steatosis, downstages hepatic fibrosis without worsening steatohepatitis (in combination with firsocostat) | Phase II study | 29 |
| | Tropifexor | Not specified | Dose responseon liver enzyme elevations and hepatic fat fraction | Randomized, multicenter, double-blind phase 2 study | 30 |
| | Vonafexor | Not specified | Reduces body weight, liver enzymes, and liver fat content | LIVIFY phase IIa study | 31 |
| PSC | OCA | 1.5–3 mg or 5–10 mg | Reduces ALP levels by 14%–25%, depending on dose and concomitant use of UDCA | Randomized controlled trial | 32 |
| | Cilofexor | 100 mg | Reduces ALP levels by 21% after 12 wk of treatment | Phase II clinical trial | 33 |

ALP, alkaline phosphatase; FLINT, Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis; NAFLD, nonalcoholic fatty liver disease; OCA, obeticholic acid; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; REGENERATE, Randomized Global Phase 3 Study to Evaluate the Impact on Non-alcoholic steatohepatitis, With Fibrosis of Obeticholic Acid Treatment; UDCA, ursodeoxycholic acid.

and close monitoring of liver function tests are crucial when using this medication.[35] As such, in 2021, the Food and Drug Administration issued a warning restricting its use in patients with advanced cirrhosis, and subsequently, the American Association for the Study of Liver Diseases updated its guidance.[36,37]

## Nonalcoholic Fatty Liver Disease

NAFLD is a common liver disease characterized by the accumulation of fat in the liver in the absence of excessive alcohol consumption. NAFLD is closely associated with obesity, type 2 diabetes, and metabolic syndrome. There are no approved therapies for NAFLD, and lifestyle modifications are the mainstay of therapy. FXR agonists have shown promise in the treatment of NAFLD by improving liver function, reducing hepatic steatosis, and improving insulin sensitivity in preclinical studies.[38] Several FXR agonists are being evaluated in clinical trials for the treatment of NAFLD (Table). A proof-of-concept trial showed that OCA was well tolerated in patients with NAFLD and type 2 diabetes and had improvement in insulin sensitivity and markers of liver inflammation and fibrosis.[39] In the multicenter randomized placebo-controlled trial, Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis, OCA was shown to improve NAFLD histologically in 45% of patients when compared to 23% in the placebo group over a period of 72 weeks.[27] This was the first study to demonstrate that FXR activity may be an important target in improving the histologic activity of NAFLD. In the interim analysis of a large ongoing clinical trial, the Randomized Global Phase 3 Study to Evaluate the Impact on Non-alcoholic steatohepatitis With Fibrosis of Obeticholic Acid Treatment Study, OCA resulted in improvement in fibrosis as well as steatohepatitis activity in a dose-dependent manner over a period of 18 months.[28] There are many other FXR agonists that are currently under investigation for the treatment of NAFLD, including cilofexor and tropifexor, among others, which show some promise in few trials to reduce steatosis as well as fibrosis. Cilofexor was shown in a phase II study to downstage hepatic fibrosis without worsening of steatohepatitis when used in combination with firsocostat (an acetyl CoA carboxylase inhibitor).[29] Tropifexor was evaluated in a randomized, multicenter, double-blind, three-part adaptive design phase 2 study in patients with nonalcoholic steatohepatitis and showed a dose response on liver enzyme elevations and hepatic fat fraction.[30] Another FXR agonist, vonafexor, was evaluated in the LIVIFY trial, a double-blind phase IIa study conducted in patients with suspected

fibrotic non-alcoholic steatohepatitis. It was generally well-tolerated, and the highest dose of vonafexor was associated with significant reductions in body weight, liver enzymes, and liver fat content on magnetic resonance imaging.[31] Other preclinical studies continue to evaluate the use of dual FXR and other receptor agonists such as FGF15 and TGR5, as well as the use of combination therapy with UDCA on the development of NAFLD in mouse models.[40–42] However, while FXR agonists in experimental settings may improve insulin resistance, clinical trials such as Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis and Regenerate have shown mixed results. In these trials, some patients with non-alcoholic steatohepatitis experienced worsened insulin sensitivity, indicating that the relationship between FXR agonists and insulin resistance may be more complex than initially thought. This highlights the need for further research to fully understand the role of FXR agonists in the management of insulin resistance in patients with NAFLD.[27,28]

## Inflammatory Bowel Disease

IBD is a chronic inflammatory disorder of the intestine that includes Crohn's disease and ulcerative colitis. IBD is associated with dysregulated immune responses and alterations in the gut microbiota. FXR agonists have shown immunomodulatory effects that may be beneficial in the management of IBD. Bile acids play a significant role in triggering intestinal inflammation and cell death. However, FXR helps regulate bile acid homeostasis and prevent toxicity.[43,44] Studies have shown that decreased FXR activity is associated with the development of IBD in both humans and animal models.[45,46] In the inflamed colonic mucosa of IBD patients, decreased FXR activity leads to altered primary bile acid biosynthesis, which results in increased inflammation and cell death in the intestinal mucosa.

Recent studies have highlighted the potential of FXR as a therapeutic target for IBD. Treatment with mesenchymal stem cell-derived exosomes has been found to restore colonic FXR expression and improve gut microbiota in a mouse model of IBD, leading to a reduction in IBD symptoms.[47,48] In animal models of colitis, the intestines of FXR-deficient mice display a more severe proinflammatory and profibrotic state, accompanied by immune dysfunction. Treatment with OCA effectively inhibits colitis in wild-type mice but not in FXR-deficient mice.[49] The activation of FXR also reduces goblet cell loss, protects the intestinal barrier, and inhibits the inflammatory response, which leads to the prevention of colon shortening and weight loss.[50]

However, excessive activation of NF-$\kappa$B in IBD patients leads to FXR inhibition and suppression of its target genes such as SHP, IBABP, and FGF15/19, which can contribute to inflammation and epithelial barrier dysfunction.[50–53] Conservative NF-$\kappa$B binding sites are also found in the promoter of the FXR target gene, indicating a close relationship between the 2 pathways.[54] Therefore, the regulation of FXR activity can have unintended effects in IBD treatment, and the use of FXR agonists must be carefully considered.

Overall, FXR agonists may have potential as therapeutic agents for IBD, with the ability to reduce inflammation, improve intestinal barrier function, and regulate bile acid homeostasis. However, further studies are needed to determine the long-term safety and efficacy of FXR agonists in IBD treatment, as excessive activation of FXR can have negative consequences in the presence of excessive NF-$\kappa$B activation. To date, there has not been a clinical trial that assesses the usefulness of any FXR agonist in IBD patients.

## Alcohol-Related Liver Disease (ALD)

Alcohol-induced disruption of the enterohepatic circulation has been linked to decreased activity of the nuclear receptor FXR. Chronic alcohol consumption results in FXR inactivation due to increased acetylation of FXR, which may be potential pharmacological targets for alleviating alcohol-induced cholestasis and liver injury.[55–57]

Pharmacological activation of FXR by specific agonists such as WAY and 6ECDCA attenuated chronic alcohol-induced liver injury and steatosis by decreasing lipogenesis through the SHP-LXR axis, ablating SREBP1-mediated lipogenesis, and reducing oxidative stress. Additionally, FXR activation induced expression of ADH1A and ADH1B, resulting in increased ADH1 enzymatic activity, which may play a protective role against human alcohol-related liver disease (ALD). Conversely, ablation of FXR exacerbated alcohol-induced liver injury likely by regulating lipid metabolism, sensitivity to inflammation, and CYP2E1-mediated oxidative stress.[56,58–60]

The gut microbiome plays a critical role in ALD with bacterial overgrowth and dysbiosis being hallmarks of various liver diseases, including ALD.[61–63] ALD patients exhibit bacterial overgrowth along the GI tract, which affects alcohol metabolism, resulting in an increased concentration of acetaldehyde.[64–67] Endotoxemia is well-documented in patients with ALD, and it increases hepatic inflammation due to activation of Kupffer cells and subsequent toll-like receptor 4-mediated cytokine and chemokine production.[63,68] Alcohol exposure induces bacterial translocation and increases gut permeability, promoting endotoxemia and facilitating the development of ALD.[63] The gut microbiota also plays an essential role in bile acid metabolism, with chronic alcohol consumption increasing the concentration of unconjugated bile acids along the GI tract, particularly in the small intestines, and decreasing the concentration of taurine-conjugated bile acids.[69] This perturbed bile acid profile may be due to gut bacterial overgrowth, resulting in increased deconjugation of bile acids and taurine metabolism.[63] Activation of FXR by bile acids induces expression of genes involved in enteroprotection and inhibits bacterial overgrowth and mucosal injury, while FXR knockout mice display more severe bacterial overgrowth and epithelial barrier deterioration.[3]

Further research is required to investigate the involvement of FXR and bile acids in alcohol-induced hepatotoxicity and steatosis, as FXR-bile acid axis appears to hold potential as a therapeutic target for ALD.

### *Primary Sclerosing Cholangitis (PSC)*

FXR agonists have also been investigated in PSC. In a Phase II clinical trial of PSC patients without cirrhosis and with elevated ALP levels, cilofexor demonstrated a 21% reduction in ALP levels after 12 weeks of treatment with a daily dose of 100 mg.[33] In a randomized controlled trial, OCA was also found to reduce ALP levels in PSC patients by 14%–25%, depending on the dose (1.5–3 mg daily or 5–10 mg daily) and concomitant use of UDCA[32] (Table). These findings suggest that FXR agonists may provide a novel therapeutic approach for PSC patients, although further research is needed to determine the long-term effects and potential side effects of these treatments.

## Safety, Adverse Effects, and Drug Interactions of FXR Agonists

Like any other pharmacological agent, FXR agonists are not without adverse effects. However, their side effect profile is generally well tolerated by patients. OCA has been associated with adverse effects such as pruritus and fatigue, which may limit its use. After a three-year follow-up period of patients with PBC on OCA, up to 77% of patients developed pruritis, and 33% developed fatigue.[23] Other side effects include GI symptoms such as diarrhea, abdominal discomfort, and bloating. These effects are typically mild and self-limited and can be managed with dose reduction or discontinuation of the drug.

On the other hand, nonsteroid FXR agonists are being developed and studied for their potential to offer similar therapeutic benefits with fewer side effects. They may provide a more favorable safety profile, particularly in terms of hepatotoxicity, which is a concern with steroid-based FXR agonists.[70]

Overall, FXR agonists are considered to be relatively safe and well-tolerated by patients with GI diseases. However, clinicians should be aware of the potential for adverse effects and drug interactions and should take appropriate steps to minimize these risks.

## Summary

In summary, FXR agonists have emerged as a promising therapeutic strategy for the management of various GI diseases, including PBC, NAFLD, IBD, ALD, and PSC. These agents exert their beneficial effects through the regulation of bile acid, lipid, and glucose metabolism, as well as immunomodulatory effects on the innate immune system. Clinical evidence has demonstrated the efficacy of FXR agonists, such as OCA, in improving liver function, reducing hepatic steatosis, and improving histological endpoints in patients with PBC and NAFLD. While the potential therapeutic benefits of FXR agonists in IBD, ALD, and PSC have been suggested by preclinical and early-phase clinical studies, further research is needed to determine their long-term safety and effectiveness in these diseases.

Despite their generally favorable safety profile, FXR agonists can be associated with adverse effects such as pruritus, fatigue, and GI symptoms. Clinicians should be aware of these potential side effects and manage them appropriately through dose reduction or discontinuation, if necessary. Additionally, the potential for drug interactions should be considered when prescribing FXR agonists.

## Conclusion

FXR agonists represent a novel and promising therapeutic approach for the management of various GI diseases. Their ability to regulate critical metabolic processes such as bile acid, lipid, and glucose metabolism and their immunomodulatory effects on the innate immune system make them an attractive option for the treatment of GI diseases. As clinical evidence supporting the efficacy of FXR agonists in these conditions continues to grow, they may become a more prominent component of the therapeutic arsenal employed by clinicians to manage these disorders.

However, further research, including long-term studies and evaluations of their safety and effectiveness in a broader range of GI diseases, is necessary to fully understand the potential of FXR agonists as a treatment option. In addition, the development of next-generation FXR agonists with improved potency and reduced side effects could further enhance their therapeutic potential. Ultimately, the continued investigation and optimization of FXR agonist-based therapies hold great promise for improving the lives of patients suffering from GI diseases.

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This author discloses the following: Fredric D. Gordon is a member of the Board of Editors. Their paper was handled in accordance with our conflict of interest policy. See https://www.ghadvances.org/content/authorinfo#conflict_of_interest_policy for full details. The remaining author discloses no conflicts.

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