



Fibrates for the treatment of pruritus in primary biliary cholangitis: a systematic review and meta-analysis

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Background: This meta-analysis aimed to evaluate the effectiveness of fibrates in the treatment of pruritus in patients with primary biliary cholangitis (PBC), so as to guide the clinical treatment of such cases.

Methods: Searches of the PubMed, Google Scholar, and Cochrane Library databases were performed to identify randomized controlled trials (RCTs) and prospective studies published up to December 2020 that used bezafibrate and fenofibrate as treatments for pruritus in patients with PBC. Data extraction and quality evaluation of the included literature were performed. Review Manager 5.3 software was employed for statistical analysis of the data.

Results: This meta-analysis included 7 studies, comprising 382 patients with PBC, which assessed the efficacy of bezafibrate and fenofibrate for treating pruritus. The results showed that treatment with fibrates significantly improved pruritus symptoms in patients with PBC [relative risk (RR) =6.52, 95% confidence interval (CI): 3.26–13.06, $P<0.00001$]. Subgroup analysis revealed that in comparison with fenofibrate (RR =5.34, 95% CI: 0.88–32.62, $P=0.07$), bezafibrate (RR =25.87, 95% CI: 7.93–84.42, $P<0.00001$) was more effective in improving pruritic symptoms in patients with PBC. Bezafibrate was also superior to fenofibrate in reducing the degree of pruritus in patients (mean difference =3.36, 95% CI: 2.62–4.09, $P=0.05$, $I^2=73\%$).

Conclusions: Fibrates can significantly improve pruritus symptoms in patients with PBC but only in a subset of patients. Further studies are needed to elucidate the pathophysiological mechanisms underlying the effect of fibrates on pruritus in PBC, and thus guide future treatment regimens.

Keywords: Primary biliary cholangitis (PBC); pruritus; bezafibrate; fenofibrate

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Introduction

Primary biliary cholangitis (PBC), formerly known as primary biliary cirrhosis (1), is a chronic autoimmune liver disease. PBC predominantly affects women over 30 years old, and its global prevalence varies from 1.9 to 40.2 per 100,000 people (2-4). This disease entails the characteristics of positive serum autoantibodies, inflammation and

destruction of the intrahepatic small bile duct, and progressive cholestasis with pruritus as a hallmark symptom, as well as slow progression to cirrhosis and liver failure (5,6). In PBC, pruritus is a common complication, which is developed by 70% of patients during the course of their disease (7).

In patients with PBC, cholestatic pruritus has a complex pathogenesis. Several proposed causes of pruritus,

including increased concentrations of bile salts, histamines, progesterone metabolites, or endogenous opioids (8,9), remain controversial. Due to the pathogenesis being unknown, current antipruritic treatment can only aid in alleviating patients' symptoms. A previous study carried out an evaluation of patients with PBC-induced pruritus, mainly using visual analogue scale (VAS) and numeric rating scale (NRS) scores (10). However, as the evaluation of pruritus is influenced by subjective factors, and the evaluation criteria and primary endpoints differ, it is still difficult to diagnose pruritus objectively or compare the clinical trial results of pruritus treatments and changes in pruritus intensity.

Several interventions to relieve the pruritic symptoms of patients with PBC have been tested (11). New therapeutic targets have recently been discovered based on advances in the understanding of the pathophysiology of hepatic pruritus. The results of drug trials of kappa opioid receptor and peroxisome proliferator-activated receptor (PPAR) agonists, as well as ileum bile acid transport inhibitors (8,11), have confirmed these targets. However, there is currently no widely accepted or effective novel treatment for pruritus in patients with PBC, despite its high prevalence and impact on patients' quality of life.

In the quest to discover appropriate treatments for pruritus, fibrates represent a promising option for future antipruritic therapy. Herein, we conducted a meta-analysis to evaluate the effectiveness of fibrates in the treatment of PBC-induced pruritus, so as to guide the clinical treatment of patients with PBC. We present the following article in accordance with the PRISMA reporting checklist (available at <https://dx.doi.org/10.21037/apm-21-1304>).

Methods

Literature retrieval

The PubMed, Google Scholar, and Cochrane Library databases were searched to identify relevant articles published up to December 2020, with the language being limited to English. Keywords, used in various combinations, included "primary biliary cholangitis", "randomized controlled trial", "pruritus", "itching", "bezafibrate", and "fenofibrate".

Inclusion and exclusion criteria

The inclusion criteria were as follows: (I) randomized controlled trials (RCTs) or prospective studies; (II)

articles comparing the efficacy of fibrates with placebo/no treatment for pruritus in patients with PBC; (III) English-language publications; and (IV) human participants.

Cross-over experiments, redundant publications including duplicates, and trials not focusing on pruritus in the main results were excluded.

Literature quality evaluation

Data on the study design, study population, intervention, clinical efficacy, and adverse events (AEs) were extracted from the included studies. The proportion of patients with pruritus and the use of scales (such as VAS, PCB-40 which is a disease-specific questionnaire for the quality of life, and 5-D Itch Scale) to assess changes in pruritus intensity were selected for the results analysis. The Cochrane risk-of-bias assessment tool was used to independently assess the quality of each article (12). This tool takes into account items including the adequacy of sequence generation, allocation concealment, blinding, completeness of outcome data, selective reporting, and other sources of bias. According to the above items, the included studies were classified as having a high, low or unclear risk of bias.

Statistical analyses

Review Manager 5.3 (International Business Machines Corporation, China) was employed for statistical analysis. For dichotomous variables, risk ratios (RRs) were calculated; for continuous variables, mean difference (MDs) were analyzed. All data were analyzed within the 95% confidence interval (CI). Heterogeneity was detected using the chi-square test or I^2 test. If $I^2 \geq 50\%$ or $P \leq 0.05$, heterogeneity was considered to exist, and the random-effects model (REM) was used. If $I^2 < 50\%$ and $P > 0.05$, heterogeneity was considered to be absent, and the fixed-effects model (FEM) was used. Additionally, in cases of significant heterogeneity, subgroup or sensitivity analysis was carried out.

Results

Quality evaluation and basic characteristics of the included articles

The search strategy initially yielded 654 published articles. After screening these articles against the criteria and reading the titles, abstracts, and full texts, we finally obtained 7 eligible RCTs and prospective studies for the meta-analysis

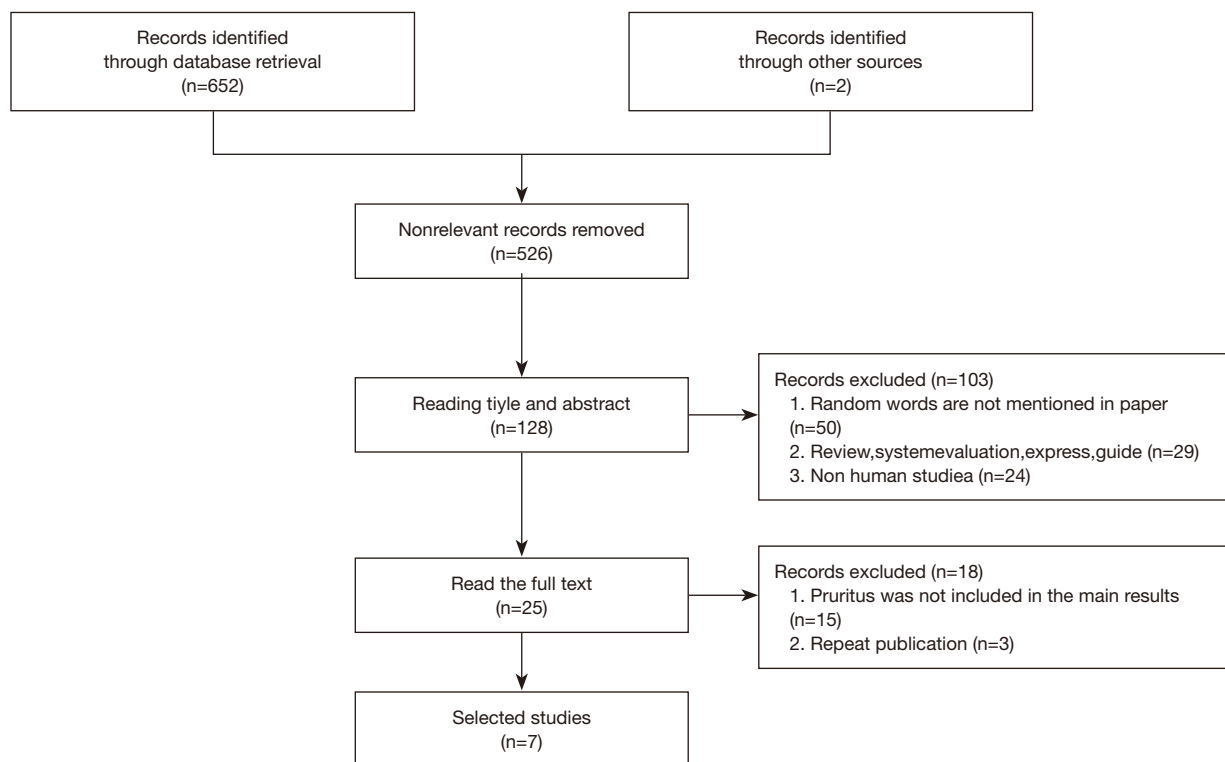


Figure 1 PRISMA flow diagram for the literature retrieval process.

(Figure 1). These 7 studies included 382 patients (average age: 53.0 years; 93.2% female). In 6 of the studies, patients with an inadequate response to ursodeoxycholic acid (UDCA) received fibrates or a placebo while continuing UDCA treatment (13-18). One pilot study measured changes in patients who were given UDCA and bezafibrate at 3-month intervals during a study period of 12 months, at 3 months after discontinuing bezafibrate, and at 3 months after resuming bezafibrate (19). *Table 1* shows the baseline characteristics of all the studies. Using the Cochrane risk-of-bias tool, 4 of the 7 articles were assessed as having a low risk of bias overall (Figure 2A,B).

Meta-analysis results

Pruritus

Seven studies (13-19) recorded the clinical symptoms of pruritus. Among them, 5 articles (13-16,19) separately recorded the changes in the number of patients with pruritus, and 2 studies (17,18) recorded both the number of pruritus patients and pruritus scoring systems.

Heterogeneity assessment of the 7 articles showed $P=0.67$

and $I^2=0\%$; consequently, an FEM was adopted. Compared with placebo/no intervention (after discontinuation), fibrates were more effective in improving pruritic symptoms in patients with PBC (RR =6.52, 95% CI: 3.26–13.06, $P<0.00001$) (Figure 3A). Further, subgroup analysis of bezafibrate and fenofibrate showed that bezafibrate (RR =25.87, 95% CI: 7.93–84.42, $P<0.00001$) was more effective than fenofibrate (RR =5.34, 95% CI: 0.88–32.62, $P=0.07$) in terms of improving pruritic symptoms in patients with PBC (Figure 3B).

Heterogeneity assessment of 2 included articles that recorded both the number of pruritus patients and pruritus score (17,18) showed $P=0.05$ and $I^2=73\%$; therefore, an REM was utilized. The result revealed that bezafibrate could reduce the pruritic degree of patients with PBC (MD =3.36, 95% CI: 2.62–4.09, $P<0.00001$) (Figure 4).

AEs

All 7 articles reported on AEs. No major AEs were recorded in relation to bezafibrate therapy. The AEs reported were mild and included gastrointestinal discomfort as nausea or heartburn, and transitory myalgia with no increase

Table 1 Characteristics of the included studies

Study	Design	Population	Sample size	Intervention	Outcomes	Follow-up (months)
Kanda, 2003, (13)	RCT	Biopsy-proven PBC, mean age of 56 years, 86% female	11 bezafibrate, 11 untreated	Bezafibrate (400 mg/d)	No. of patients with pruritus	6
Levy, 2011, (14)	Prospective cohort	AMA PBC, mean age of 56 years, 80% female	20 fenofibrate	Fenofibrate (160 mg/d)	VAS, no. of patients with pruritus	12
Han, 2012, (15)	Prospective cohort	Biopsy-proven + AMA PBC, mean age of 51 years, 91% female	22 fenofibrate + UDCA, 22 UDCA	fenofibrate (200 mg/d)	No. of patients with pruritus	3
Lens, 2014, (19)	Prospective cohort	Biopsy-proven PBC, mean age of 53 years, 100% female	28 bezafibrate	Bezafibrate (400 mg/d)	No. of patients with pruritus, pruritus score	12
Cheung, 2016, (16)	Prospective cohort	Biopsy-proven + AMA PBC, mean age of 53 years, 94% female	46 fenofibrate + UDCA, 74 UDCA	fenofibrate (145 mg/d), UDCA 13–15 mg/kg/d	No. of patients with pruritus	11
Reig, 2018, (17)	Prospective cohort	Biopsy-proven + AMA PBC, mean age of 53 years, 94% female	48. 26 treated, 26 untreated	Bezafibrate/placebo (400 mg/d), UDCA 13–15 mg/kg/d	VAS, 5-D	38
Corpechot, 2018, (18)	RCT	Biopsy-proven PBC, mean age of 53 years, 95% female	50 bezafibrate, 50 placebo	Bezafibrate/placebo (400 mg/d), UDCA 13–15 mg/kg/d	VAS	24

RCT, randomized controlled trial; UDCA, ursodeoxycholic acid; AMA, anti-mitochondrial antibody; VAS, visual analog scale (0–10); and 5-D, descriptive pruritus scale.

in muscle enzymes (13,17–19). One study stated that 1 patient in the bezafibrate group experienced a drop in their estimated glomerular filtration rate (eGFR) to under 60 mL per minute; however, this case can be excluded, as the patient had a history of diabetes and hypertension (19). Heterogeneity assessment of the 4 articles (13,17–19) focusing on bezafibrate treatment showed $P=0.10$ and $I^2=57\%$; therefore, an REM was employed for analysis. In comparison with the placebo/untreated (after discontinuation) group, patients who received bezafibrate had a significantly increased risk of AEs (RR =2.06, 95% CI: 0.33–12.80, $P=0.44$) (Figure 5A).

The 3 studies which focused on fenofibrate treatment alone reported heartburn and esophagitis as the most frequent and severe side effects of fenofibrate (14–16). Heterogeneity assessment of these 3 articles showed $P=0.39$ and $I^2=07\%$; therefore, an REM was used. In comparison with the placebo/untreated group, patients in the fenofibrate group had a lower risk of AEs (RR =19.68, 95% CI: 3.45–112.16, $P=0.0008$) (Figure 5B). However, the numbers of patients in the studies on fenofibrate therapy were insufficient, so the results require further

confirmation.

Discussion

Pruritus is a high-incidence and troublesome PBC complication that impacts patients' quality of life (20,21), and can occur at any stage of the disease. For some patients, pruritus is mild and tolerable, whereas for others, pruritus limits daily life and leads to severe sleep deprivation, fatigue, depression, and even suicidal tendencies (22). In rare cases, refractory pruritus may become the main indication for liver transplantation, even in cases without liver failure (23). In a recent report in the United Kingdom (24), 73.5% of 2,194 patients with PBC developed pruritus at some stage of the disease with 1/3 reporting persistent pruritus. Considering the prevalence of pruritus in PBC, this meta-analysis was carried out with the aim of determining the therapeutic effect of fibrate use on pruritus in patients with PBC. We found that fibrates significantly improved PBC-associated pruritus, but only in a subset of patients.

In many studies, UDCA, as a first-line drug for PBC, cannot relieve pruritus (8). Additionally, second-line (rifampin,

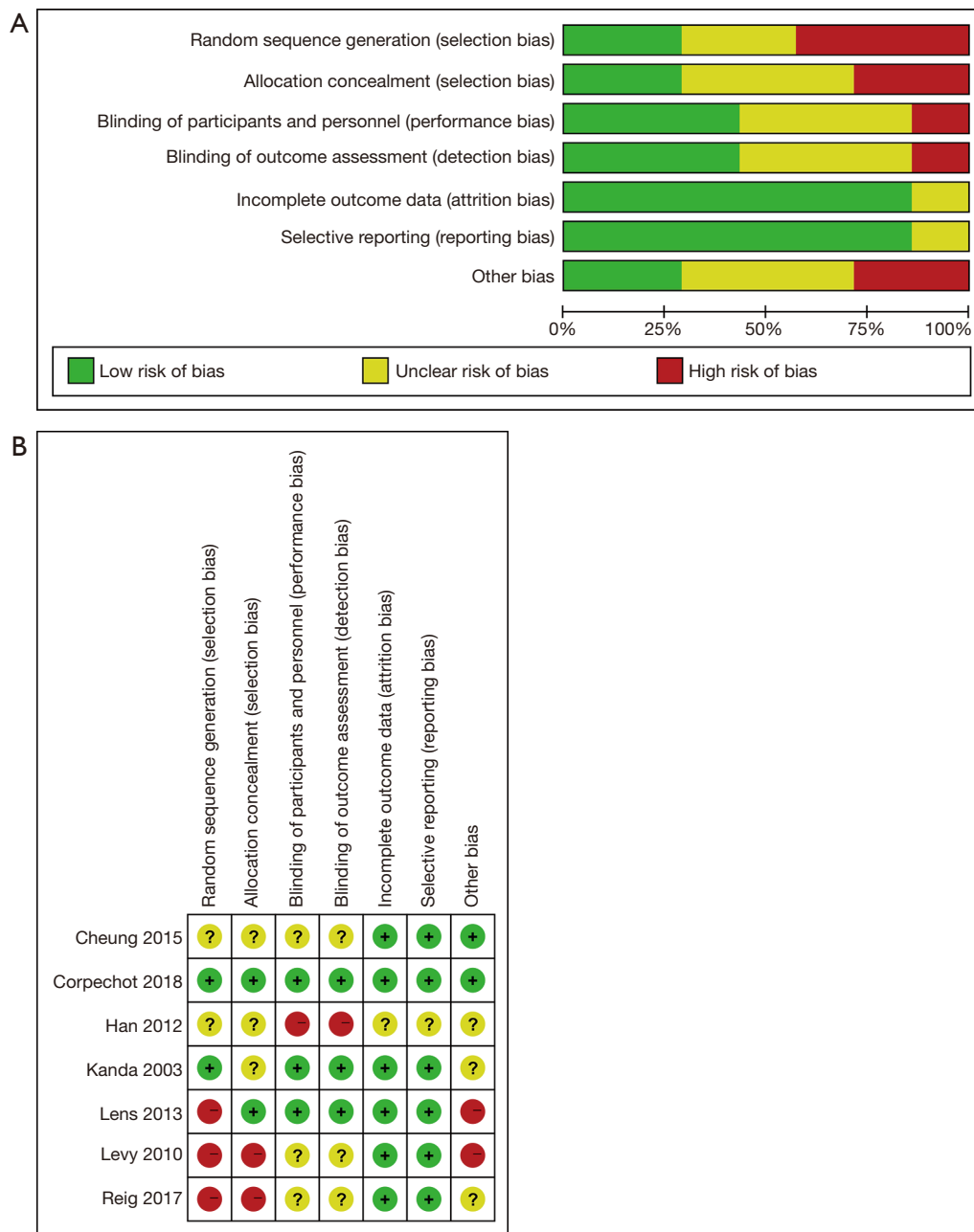


Figure 2 Quality of the included studies. (A) Overall and (B) study-level risk of bias, using Cochrane’s risk-of-bias assessment tool. Outcomes are presented as percentages of all included studies and of each included study.

a progesterone X receptor agonist), third-line (naltrexone, a pure opioid antagonist), and fourth-line (sertraline, a selective serotonin reuptake inhibitor) drugs are commonly used to treat pruritus. Unfortunately, rifampin is associated with a high rate of liver damage (5–13%) (25), resistance can develop after taking naltrexone (26), and adverse reactions to sertraline

can be severe (27). Fibrates are PPAR- α agonists and are used primarily for dyslipidemia. Many studies have reported that fibrates can ameliorate cholestatic liver disease through transcriptional activation of multidrug resistance protein 3, in addition to the other reported beneficial effects of PPAR- α activation in the liver (28). Here, we focused on the use of

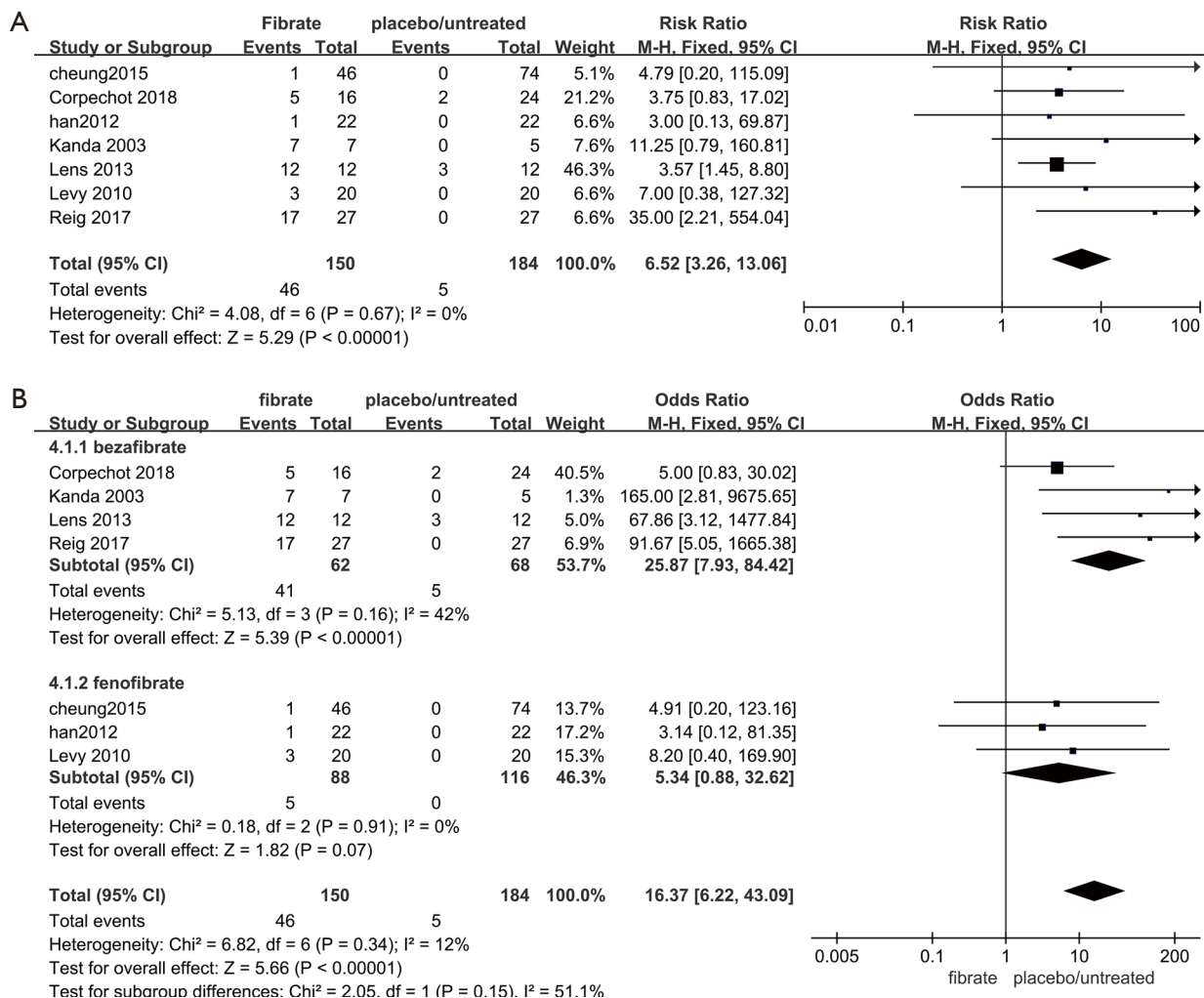


Figure 3 Comparison of the numbers of patients with pruritus treated with different treatment methods. (A) Comparison of the numbers of patients with pruritus treated with fibrates and placebo/untreated. (B) Comparison of the numbers of patients with pruritus treated with bezafibrate, fenofibrate, and placebo/untreated.

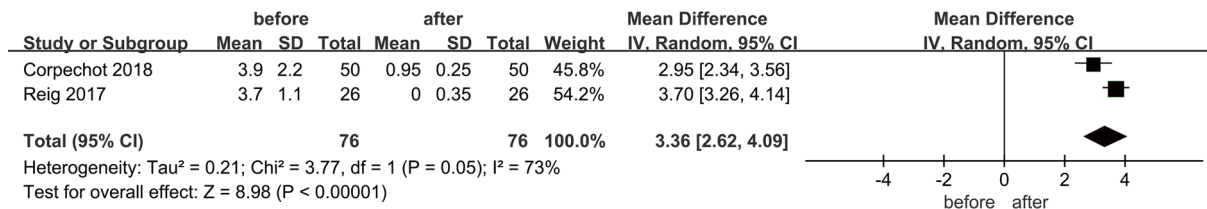


Figure 4 Comparison of pruritus scores of patients evaluated using the visual analog scale before and after bezafibrate treatment.

fibrates in the treatment of pruritus in patients with PBC, and found that bezafibrate and fenofibrate could improve the condition of these patients. Based on the case number, pruritus

degree, and incidence of AEs, bezafibrate was found to have a stronger effect on pruritus in PBC.

The relevant physiological and pathological mechanisms

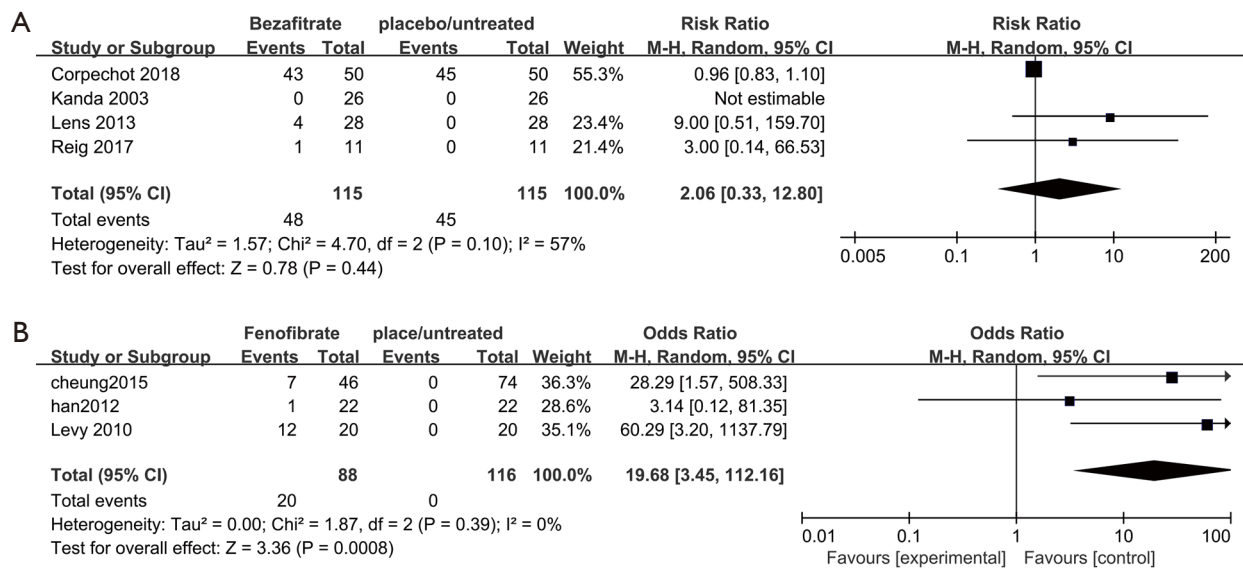


Figure 5 Number of adverse events in patients treated with bezafibrate and fenofibrate. (A) Number of adverse events in patients treated with bezafibrate. (B) Number of adverse events in patients treated with fenofibrate.

of the existing treatment options for pruritus have not been effectively proven. The pathogenesis of pruritus in patients with PBC is complex, which is different from other types of pruritus, and several proposed causes of pruritus remain controversial. In one study (29), 175 DNA samples from patients with PBC in Italy and the United States suggested that A118G in the OPRM1 gene sequence may protect patients from pruritus. In another study (30), v1188e in multidrug resistance-associated protein 2 was reported to alter the pruritus-related factors and its cofactors from hepatocytes into bile or the central nervous system, thereby influencing the degree of pruritus in patients. Recently, lysophosphatidic acid, a powerful neuronal activator, has been evidenced as a potential cause of cholestatic pruritus (16). Because the pathogenesis of pruritus is unknown, the current antipruritic treatment strategy can only alleviate the symptoms of some patients. The latest research shows that even with an incomplete biochemical response, patients treated with bezafibrate still benefit from reduced risk of death or liver transplantation and therefore, should not discontinue this medication (31). These findings also evidence an important role of fibrates in the treatment of PBC, which is consistent with our meta-analytical results.

Still, our meta-analysis has some limitations. First, most of the trials included in this study did not use effective pruritus assessment tools. Pruritus in patients with PBC characteristically affects the limbs, especially the hands and

feet, and other parts of the body. Usually, the symptoms of pruritus follow a circadian rhythm, strongly appearing in the evening and at night (32). Due to the subjectivity of pruritic assessment, the evidence to support the results of the trials is poor quality. Second, although some included trials did report on patient compliance, no statistics on compliance among the pruritus population were given. Thus, it was unclear whether or not the patients with pruritus were less compliant with treatment than patients without pruritus. Hence, future studies should use pruritus assessment tools such as VASs which have been validated to be relatively objective, to ensure that the drug compliance of pruritus patients is not a confounding factor.

Pruritus is a major factor affecting the quality of life of patients with PBC. Doctors and patients are hoping that an effective strategy for the treatment and management of pruritus is identified. This study found that fibrates could improve pruritus in patients with PBC, but only in a subset of patients. This finding suggests that fibrates cannot actually treat the underlying causes of PBC-related pruritus. Therefore, further studies are needed to uncover the pathophysiological mechanism of pruritus in PBC in order to identify a promising antipruritic treatment plan for patients.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/apm-21-1304>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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