Digestive Diseases and Sciences (2023) 68:2710–2730
https://doi.org/10.1007/s10620-023-07862-z

ORIGINAL ARTICLE

Cholestatic Pruritus Treatments in Primary Biliary Cholangitis and Primary Sclerosing Cholangitis: A Systematic Literature Review

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Received: 16 September 2022 / Accepted: 30 January 2023 / Published online: 18 March 2023

Abstract

Background and Aims We conducted a systematic literature review to understand the evidence supporting treatment decisions for cholestatic pruritus associated with primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC).

Methods Studies that enrolled ≥ 75% participants with PBC or PSC and reported ≥ 1 endpoint(s) related to efficacy, safety, health-related quality of life (HRQoL) or other patient-reported outcomes were included. Bias was assessed using the Cochrane risk of bias tool for randomised controlled trials (RCTs) and the Quality of Cohort studies tool for non-RCTs.

Results Thirty-nine publications were identified, covering 42 studies and six treatment classes (including investigational and approved products): anion-exchange resins, antibiotics (rifampicin/derivatives), opiates, selective serotonin reuptake inhibitors, fibrates, ileal bile acid transporter inhibitors and other agents not categorised in these six classes. Across studies, median sample size was small ($n = 18$), 20 studies were over 20 years old, 25 followed patients for ≤ 6 weeks, only 25 were RCTs. Pruritus was assessed using several different tools, with inconsistencies in their application. Cholestyramine, considered first-line therapy for moderate-severe cholestatic pruritus, was assessed in six studies (two RCTs) including 56 patients with PBC and 2 with PSC, with evidence of efficacy demonstrated in only three studies, among which, two RCTs were assessed as having a high risk of bias. Findings were similar for other drug classes.

Conclusions There is a lack of consistent and reproducible evidence available on efficacy, impact on HRQoL, and safety of cholestatic pruritus treatments, leaving physicians to rely on clinical experience rather than evidence-based medicine for treatment selection.

Keywords Cholestatic pruritus · Primary biliary cholangitis · Primary sclerosing cholangitis · Treatment decisions · Quality of life · Evidence-based medicine

Abbreviations

AE	Adverse event
DEAE	Diethylaminoethyl
HRQoL	Health-related quality of life
IBAT	Ileal bile acid transporter
ICTRP	International Clinical Trials Registry Platform
ISRCTN	International Standard Randomised Controlled Trial Number
PBC	Primary biliary cholangitis
NIH	National Institutes of Health
NRS	Numerical rating scale
PPAR	Peroxisome proliferator-activated receptor

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PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcome
PSC	Primary sclerosing cholangitis
Q-Coh	Quality of Cohort Studies
RCT	Randomised controlled trial
SF-36	36-Item Short Form survey
SSRI	Selective serotonin reuptake inhibitor
UDCA	Ursodeoxycholic acid
VAS	Visual analogue scale
WHO	World Health Organization

Introduction

Cholestatic pruritus is a common and debilitating condition associated with autoimmune liver diseases, such as primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) [1]. While pruritus is experienced by approximately 70% of patients with PBC, its exact prevalence in PSC is unclear and most patients are asymptomatic at diagnosis [2, 3]. In the TARGET-PBC study of 671 patients with PBC, the presence of itching was reported in 81% of patients who had completed a PRO ($n = 211$). Of the patients with itch, 37% reported clinically significant itch [4]. Pruritus has a profoundly negative impact on health-related quality of life (HRQoL) [5–9]. Patients with clinically significant itch report significantly greater fatigue, worse cognition, and significant impacts on their emotional health, sleep and social life [4].

Current treatment options for the management of cholestatic pruritus are limited, and evidence of efficacy is equivocal [10–12]. The TARGET-PBC study reported that 52% of patients with pruritus had never received treatment for itch. [4] Cholestyramine, a bile acid-binding resin, is the recommended first-line therapy for moderate-severe cholestatic pruritus in several countries, despite a limited evidence base [13–15]. It is the only medication with an indication for the relief of pruritus associated with partial biliary obstruction in the US (approved December 1966), and for the relief of pruritus associated with partial biliary obstruction and primary biliary cirrhosis in Europe (approved July 1988) [16, 17]. Only 25% of patients with clinically significant itch were being treated with bile acid-binding resins (including cholestyramine) in the TARGET-PBC study population [4]. Nalfurafine, a κ-opioid receptor agonist, has been approved in Japan for the treatment of pruritus in chronic liver disease since 2015 [18]. Off-label options that are recommended for the treatment of cholestatic pruritus include the antibiotic, rifampicin, which targets the pregnane X receptor, opioid antagonists (naltrexone, naloxone), and the selective serotonin reuptake inhibitor (SSRI) sertraline [13, 14]. However, as with cholestyramine, there is a limited evidence base to support their use [13, 14]. Oral antihistamines are also frequently prescribed to patients with cholestatic pruritus; however, cholestatic pruritus has a diverse and complex pathogenesis that does not appear to be histamine-mediated [4, 19]. Owing to this, antihistamines are not effective in alleviating pruritus in most cases [18], but may provide some benefit to patients because of their sedative properties [14]. A systematic review of the literature in 2010 concluded that there is little objective evidence to demonstrate oral antihistamines are effective treatment of pruritus and identified only four large, good quality clinical trials to support the use of topical antihistamines. All four studies enrolled patients with pruritus of any etiology and none of the studies included patients with pruritus associated with primary biliary cholangitis. [20] Evidence to conclusively support the use of antihistamines in PBC is lacking and further high-quality clinical studies are needed. Consequently, there is a clear need for new treatments for cholestatic pruritus with supporting efficacy and safety data from well-controlled clinical trials.

More recently, clinical research has focused on the ileal bile acid transporter (IBAT) inhibitors as potential treatment options for cholestatic pruritus in PBC and PSC, including linerixibat (GSK2330672), odevixibat (A4250) maralixibat (SHP625) and volixibat (SHP626), which have all been evaluated in early phase clinical trials [21–24]. In a Phase 2a, double-blind, randomised, placebo-controlled, crossover trial in adults with PBC, 14 days of linerixibat treatment led to significant reductions in pruritus severity versus placebo [23], further supported by evidence of rapid itch improvement observed in the Phase 2b GLIMMER study [25]. Linerixibat is currently being assessed in the ongoing Phase 3 GLISTEN study in PBC (NCT04950127). Odevixibat (approved for the treatment of pruritus in progressive familial intrahepatic cholestasis in the US [26]) has demonstrated improvement in pruritus in adults with PBC [21]; however, this small pilot study was terminated early following a high incidence of abdominal adverse events (AEs) [21]. A 13-week, randomised, double-blind, placebo-controlled Phase 2 trial in adults with PBC, showed that the reductions in pruritus observed with maralixibat (recently approved for treatment of pruritus in Alagille syndrome in the US) were not significantly different compared with placebo [24]; similar to the other IBAT inhibitors, diarrhoea and abdominal pain were the most frequently reported AEs [24].

The peroxisome proliferator-activated receptor (PPAR) agonists seladelpar and elafibranor have been evaluated in Phase 2 trials in patients with PBC and inadequate response to ursodeoxycholic acid (UDCA) [27, 28]. Both were shown to improve pruritus in patients with PBC, although this was not a prespecified evaluation [28, 29]. Although both compounds also reduced levels of disease-related biomarkers, the seladelpar study was terminated early as three patients

on masked treatment developed grade 3 aminotransferase elevations (> 5–20 times the upper limit of normal) that were initially deemed to be drug related [27]. Following an expert panel review, it was found that there was no clinical, biochemical or histological evidence to support seladelpar-related liver injury [30]. Both seladelpar and elafibranor are currently being assessed in ongoing Phase 3 studies in PBC (NCT04620733 and NCT04526665, respectively). However, the PPAR agonists were not included in our current literature review, as the associated studies did not meet eligibility criteria for inclusion (see Methods).

The primary objective of this systematic literature review was to evaluate the evidence for efficacy of treatments for cholestatic pruritus associated with PBC and PSC. Impact on HRQoL and safety outcomes were assessed as secondary objectives.

Methods

Identification and Selection of Relevant Studies

A list of relevant studies was created from the bibliographies of prior literature reviews (previously conducted in-house by GSK) and was used to pilot test literature search strategies to ensure these searches returned relevant studies. These literature reviews included a broad review of treatment pathways, disease burden, clinical endpoints, and health technology authority perspectives of pruritus caused by cholestatic liver diseases and reviews focusing on symptom impact, patient-reported outcome (PRO) instruments, and psychometric properties of PROs in cholestatic pruritus.

A pragmatic literature search was also conducted to identify relevant studies using PubMed (including Medline), Embase, Cochrane CENTRAL database (which indexes both publications and trial registry data) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; which indexes the International Standard Randomised Controlled Trial Number [ISRCTN] trial registry and includes non-randomised and observational studies).

Databases, websites and hand searches identified two primary classes of data sources: publications and reports of clinical trials (including journal papers, conference abstracts, papers, posters and presentations); and clinical trial registry records. Each of these data sources was screened to identify relevant studies for inclusion. The two classes were then mapped against each other to associate records from clinical trial registries with corresponding publications and reports. Additional searches were conducted to identify relevant clinical trials from the trial registries, for which either no publication or report were found, or for which associated publications or reports did not provide adequate information to be included in the review.

Searches of PubMed, Embase and the Cochrane CENTRAL database were conducted on 31 March 2020. The WHO ICTRP search was initially conducted on 12 March 2020, but could not be repeated on 31 March 2020, owing to access restrictions imposed during the COVID-19 pandemic, and therefore the earlier search results were used.

Database searches were supplemented by hand searches of the citations of relevant studies and the previous literature reviews conducted by GSK (see above). The final stage of hand searching for reports of clinical trials identified from registries utilised Google Scholar and the Web of Science Core Collection for targeted searches of associated publications and reports. Search strategies are detailed in Supplementary Table 1 provided in Online Resource 1.

For the selection of studies for further analysis, references identified from PubMed were imported first, followed by references identified from Embase; duplicate records were automatically checked and deleted. This was followed by references identified from Cochrane and WHO ICTRP, imported in the same manner. All references were checked to ensure successful export and manually corrected for errors.

Eligibility criteria for study inclusion were as broad as possible to ensure that all relevant articles were captured due to the anticipated paucity of data given the rarity of both diseases (Supplementary Table 2 provided in Online Resource 1). Selected studies were required to include participants over 18 years of age with cholestatic pruritus, with at least 75% of participants with PBC or PSC, and could be either randomised controlled trials (RCTs) or non-randomised studies. Additionally, eligible studies were required to report at least one endpoint related to pruritus efficacy, HRQoL or other PROs, and safety. There were no restrictions on study date, type of comparison among interventions, duration of follow-up, geographical location, clinical setting, publication language, format, or status. Studies with non-pharmacologic treatments and treatments that targeted the underlying liver disease but not pruritus (e.g., UDCA, obeticholic acid, ciclosporine, methotrexate, colchicine, PPAR agonists) were excluded. Preclinical studies, reviews, letters, comments, case reports and editorials were also excluded.

Data Collection and Extraction

Screening of titles/abstracts and full text articles were conducted by two independent researchers. Any discrepancies were resolved by a third researcher as required. Data extraction was performed by one researcher and checked by a second researcher. Discrepancies were resolved by consensus between the two researchers, or by arbitration or unilateral decision by a project co-lead researcher. Key data extracted

are shown in Supplementary Table 3 provided in Online Resource 1.

Risk of Bias Assessment

In accordance with recommendations from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), RCTs were assessed using the Cochrane risk of bias tool [31]. For non-randomised studies, the Quality of Cohort studies (Q-Coh) tool was used [32]. For single-arm studies, the risk of bias was assessed using the National Institutes of Health (NIH) before–after (pre–post) study with no control group assessment tool [33]. Further information on each of these bias assessment tools is detailed in the Supplementary Methods provided in Online Resource 1.

Independent risk of bias assessment was made by two senior researchers, with disagreement resolved either by consensus, discussion or unilateral decision of a co-lead researcher. The risk of bias was assessed as unclear if there was insufficient detail reported in the study.

Results

Search Results and Study Selection

A total of 1846 unique records were identified and screened for inclusion resulting in 39 relevant publications identified for data extraction and further evaluation (Fig. 1) [15, 21, 23, 24, 34–68]. These 39 publications reported on a total of 42 studies: two publications included open-label studies alongside a separate randomised study [53, 58], while one publication included data from two trials [61].

A total of 23 different treatment interventions were reported for the treatment of cholestatic pruritus from six specific classes: anion-exchange resins (eight studies) [15,

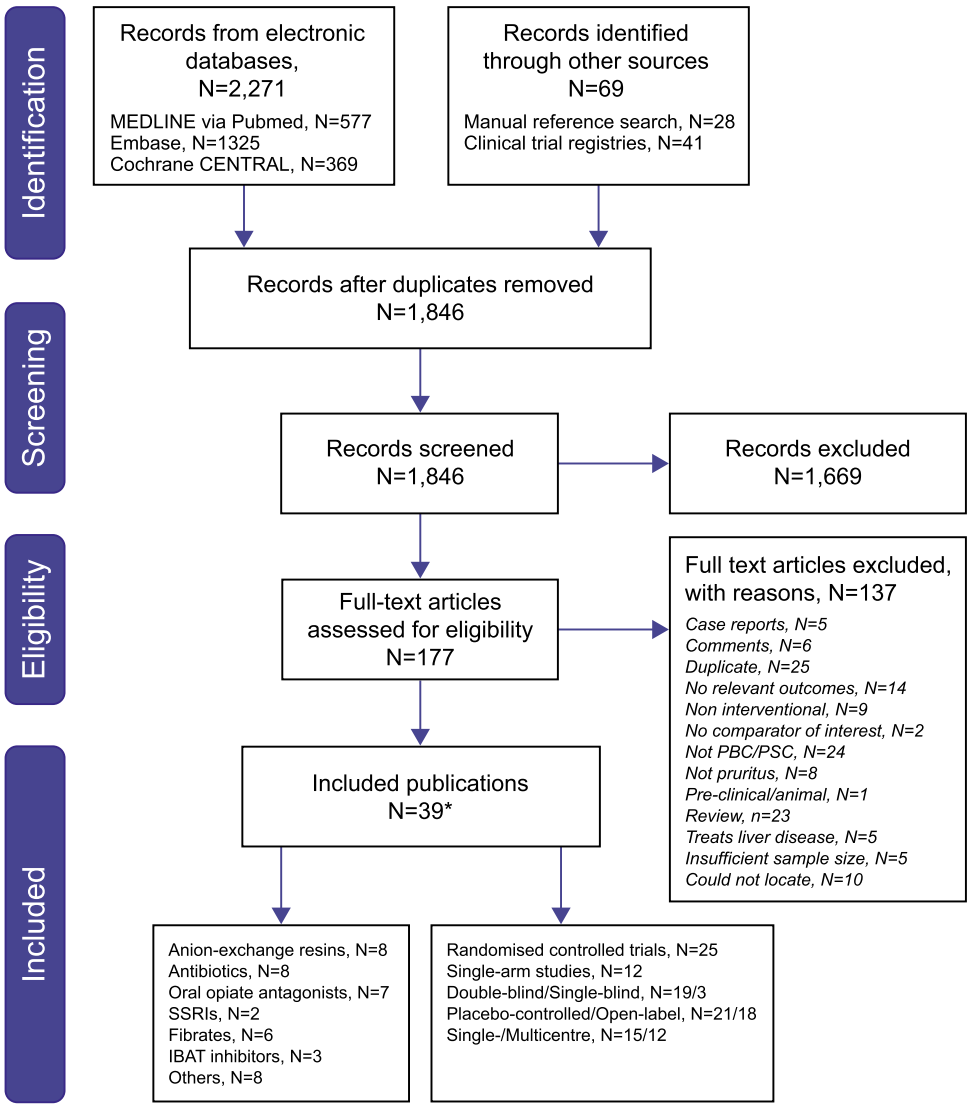

Fig. 1 PRISMA flow diagram

40–42, 45, 57, 62, 67], antibiotics (eight studies, all of which were studies of rifampicin or derivatives) [35, 36, 43, 48, 53, 56, 64], oral opiate agents (seven studies) [37, 55, 58, 59, 65, 66], the SSRI, sertraline (two studies) [34, 49], fibrates (six studies) [39, 44, 46, 47, 54, 68], IBAT inhibitors (three studies) [21, 23, 24] and others (eight studies) [38, 50–52, 60, 61, 63]. Study characteristics for each of the 42 studies eligible for inclusion are summarised in Table 1.

Risk of Bias Within Studies

The Cochrane risk of bias tool was used to assess risk of bias in 25 RCTs that met the inclusion criteria. Nearly half of these RCTs did not adequately describe the randomisation methods; however, about two-thirds were judged to be of good quality. Five trials were deemed to have a high risk of bias, while three were rated as unclear in all five domains assessed. Assessment of bias for the individual RCTs is presented in Table 2.

The Q-Coh tool was used to assess the risk of bias in three non-randomised cohort studies. The overall quality assessment was rated as acceptable for two of these studies. The remaining study was rated as low quality as 60% of the participants dropped out prior to or shortly after initiating treatment with the investigational drug.

The NIH assessment tool was used to assess the quality of 12 single-arm studies which met the inclusion criteria. Six of these studies [36, 38, 40, 48, 59, 62] were rated as fair and the remainder rated as poor. The latter studies were generally older publications that provided little or no detail on patient selection and had high rates of attrition or poorly defined measures of pruritus.

Patient Characteristics

Patient age (mean and/or median) was reported in 30/42 studies, while three studies reported the age range (Table 1). Gender was reported in 34/42 studies and was predominantly female in 31 of these studies. Overall, 23/42 studies included only patients with PBC while 3/42 studies included only patients with PSC.

Study Characteristics

Of the 42 studies identified, 20 were reported over two decades ago (pre-2000). Studies tended to be short (25 studies followed patients for ≤6 weeks with 12 studies having ≤2 weeks' follow-up) with a small sample size (median n=18). Study location was reported in 34/42 studies: 18 were in Europe; 5 in North America; 4 in Asia; 5 in South America and 2 in multiple continents. The use of combination medications was reported in 37/42 studies. UDCA was the most common medication used in these studies (19/42 studies). Concomitant treatment of pruritus was not permitted in 10/42 studies.

Pruritus Efficacy Measures

Pruritus efficacy was measured using a number of different assessments (Table 3). Pruritus numerical rating scales (NRS) were used in 10 studies, with two different pruritus NRS employed across the different studies. The first NRS included a categorical scale ranging from 0 (no itching) to 3 (severe itching) and was used in seven studies. The second NRS included a scale from 0 (no itching) to 10 (severe itching) and was used in the remaining three studies. Pruritus reduction and/or improvement was measured using a categorical outcome (e.g., complete resolution, partial resolution or worsened pruritus) in 20 studies. Ten studies provided data for the number of patients experiencing complete (i.e., disappearance) and partial (i.e., improvement) pruritus resolution; four reported data regarding partial resolution only; one reported data on complete resolution only.

A visual analogue scale (VAS) was used to assess pruritus in 20 studies. These studies utilised either a 0–10 or 0–100 VAS, usually defined in units of length (mm or cm). Half of the studies utilised a VAS scale ranging from 0 to 10 and the rest used a scale from 0 to 100.

PBC-40/PBC-27 was used in four studies. The PBC-40/PBC-27 is a questionnaire that investigates the impact of disease across six domains (fatigue, pruritus, cognitive, social, emotional, and other symptoms) and patients rate 40 or 27 items, respectively, on a scale of 0/1 to 5. All four studies reported itch domain scores at follow-up; however, only two studies reported differences versus placebo and only one study reported change from baseline.

The 5-D itch scale was used in six studies. The 5-D itch scale consists of five domains assessing the duration, degree, direction, disability, and distribution of itch with a total score ranging from 5 (no itch) to 25 (severe itch). Four studies reported absolute values, four reported change from baseline and four reported difference versus placebo.

Scratching activity was assessed in three studies. This evaluation involved activity monitoring devices with units of counts per time. Two studies reported percentage reduction in scratching activity, one of which was in terms of change from baseline, while the other was difference versus placebo. The remaining study reported absolute values at follow-up.

Interference of itch on sleep was evaluated in four studies using an NRS, medical outcomes study sleep score or a VAS. Two studies provided change from baseline data and three reported differences versus placebo. The tool for measuring sleep interference was not specified in the study by Mayo and colleagues [49].

Data related to study withdrawals due to a lack of efficacy were sparse, with only 12 of the 42 studies reporting these

Table 1 Overview of study characteristics of included studies

Study	Interventions	Study design	PBC, N (%) PSC, N (%)	Age, years	Female gender, *n* (%)	Treatment duration	Main efficacy endpoint	Concomitant medications
Anion-exchange resins (n = 8)								
Datta 1966 [40]	Cholestyramine	OL	20 (100) 0	47.6 (mean)	24 (88.9) of total (*n* = 27)	32 months (mean)	Pruritus reduction	NR
Van Berge Henegouwen 1974 [62]	Cholestyramine	Prospective, OL	6 (75) 1 (12.5)	NR	NR	5 weeks	NRS; pruritus reduction	Immunosuppressive therapy (*n* = 6 patients)
Duncan 1984 [41]	Cholestyramine vs terfenadine vs chlorpheniramine vs placebo	RCT, SB, CO, PC, SC	7 (87.5) 1 (12.5)	NR	NR	2 weeks	NRS	No antipruritic medication
Floreani 1988 [42]	DEAE-dextran vs placebo	RCT, DB, CO, PC	12 (100) 0	NR	12 (100)	15 days	Pruritus reduction	NR
Zuin 1991 [67]	Cholestyramine vs DEAE-dextran	RCT, OL, PG	30 (100) 0	NR	NR	2 months	NRS; pruritus reduction	NR
Taha 1994 [57]	Cholestyramine 4 g BID vs no treatment vs UDCA vs cholestyramine + UDCA	OL, sequential CO	8 (100) 0	52 (median)	8 (100)	2 weeks (4 phases)	VAS	UDCA
Yokomori 2001 [15]	Colestilan vs no treatment	RCT, OL, PG, SC	11 (100) 0	53.6 (mean)	9 (81.1)	4 weeks	NRS	No antipruritic medication
Kuiper 2010 [45]	Colesevelam vs placebo	RCT, DB, PG, PC, MC	14 (40) 14 (40)	52 (mean)	22 (62.9) of total (*n* = 35)	21 days	Pruritus reduction; VAS	UDCA, naltrexone (*n* = 2 patients)
Antibiotics (n = 8)								
Ghent 1988 [43]	Rifampicin vs placebo	RCT, DB, CO, PC, SC	9 (100) 0	57.4 (mean)	8 (88.9)	2 weeks (4 cycles)	VAS	Cholestyramine
Bachs 1989 [35]	Rifampicin vs phenobarbitone	RCT, CO, SC	22 (100) 0	49.7 [8.4] (mean [SD])	22 (100)	2 weeks	NRS; pruritus reduction	No antipruritic medication
Podesta 1991 [53]	Rifampicin vs placebo	RCT, DB, CO, PC, MC	14 (100) 0	43 (mean)	13 (92.9)	1 week	Pruritus reduction; VAS	No antipruritic medication
Podesta 1991 [53]	Rifampicin	OL	18 (100) 0	32 − 72 (range)			Pruritus reduction; VAS	No antipruritic medication
Bachs 1992 [36]	Rifampicin	Prospective, OL, SC	16 (100) 0	49.7 (mean)	16 (100)	11.7 months (mean)	NRS; pruritus reduction	No antipruritic medication
Loginov 1993 [48]	Rifampicin	OL	7 (100) 0	49.7 ± 2.7	7 (100)	2 weeks	Pruritus reduction	Ion-exchange resins
Tabibian 2017 [56]	Rifaximin	Prospective, OL, SC	0 (0) 16 (100)	40 (median)	3 (19)	12 weeks	5-D itch scale; fatigue	NR

Table 1 (continued)

Study	Interventions	Study design	PBC, N (%) PSC, N (%)	Age, years	Female gender, *n* (%)	Treatment duration	Main efficacy endpoint	Concomitant medications
Webb 2018 [64]	Rifampicin	Retrospective, OL, SC	36 (34.3) 44 (41.9)	Hepatitis: 37 [28–43] (median [IQR]) No hepatitis: 44 [32–59] (median [IQR])	Hepatitis: 3 (60) No hepatitis: 62 (62)	131 days (median)	NR	UDCA, proton pump inhibitors, cholestyramine, antibiotics, 5-aminosalicylic acid preps, azathioprine or 6-mercaptopurine, antihistamines, prednisolone, statins, sertraline, naltrexone
Oral opiate agents (n = 7)								
Summerfield 1980 [55]	Naloxone vs placebo	RCT, DB, CO, PC	NR NR	*n* = 20 with cholestatic liver disease (29–71 range)	13 (65)	1 night	VAS; scratching activity	Cholestyramine
Thornton 1988 [59]	Nalmefene	Prospective, OL, SC	9 (100) 0	57.2 (average)	8 (88.9)	6 months	VAS; fatigue	No antipruritic medication
Bergasa 1992 [37]	Naloxone vs placebo	SB, CO, PC	8 (100) 0	50 (average)	8 (100)	24 h	VAS; scratching activity	No antipruritic medication
Wolfhagen 1997 [65]	Naltrexone vs placebo	RCT, DB, PG, PC, SC	13 (81.3) 3 (18.8)	52 (median)	12 (75)	4 weeks	VAS; interference of itch on sleep; fatigue	No antipruritic medication
Terg 2002 [58]	Naltrexone vs placebo	RCT, DB, CO, PC, MC	15 (75) 1 (5)	55 (mean)	17 (85)	2 weeks	Pruritus reduction; VAS	UDCA, antipruritic medication
Terg 2002 [58]	Naltrexone	OL	9	36 – 70 (range)		2 months	Pruritus reduction; VAS	UDCA, antipruritic medication
Yagi 2018 [66]	Nalfurafine	Prospective, OL, MC	44 (100) 0	66.8 (mean)	39 (88.6)	12 weeks	VAS; PBC-40/ PBC-27 itch	UDCA, bezafibrate, anti-pruritic medication
Selective serotonin reuptake inhibitors (n = 2)								
Mayo 2007 [49]	Sertraline vs placebo	RCT, DB, CO, PC, SC	18 (75) 4 (16.7)	NR	28 (84.5)	6 weeks	Pruritus reduction; VAS; interference of itch on sleep	UDCA
Ataei 2019 [34]	Sertraline vs rifampicin	RCT, SB, PG, SC	13 (36.1) 23 (63.9)	41.6 (mean)	16 (44.4)	4 weeks	VAS	UDCA
Fibrate (n = 6)								
Kanda 2003 [44]	Bezafibrate vs no treatment	RCT, OL, PG, SC	22 (100) 0	56 (mean) for total (*n* = 22)	19 (86.4)	6 months	N/A	UDCA
Levy 2011 [47]	Fenofibrate	OL, MC	20 (100) 0	56 (median)	16 (80)	48 weeks	Pruritus reduction	UDCA

Table 1 (continued)

Study	Interventions	Study design	PBC, N (%) PSC, N (%)	Age, years	Female gender, *n* (%)	Treatment duration	Main efficacy endpoint	Concomitant medications
Reig 2018 [54]	Bezafibrate vs no treatment	Prospective, OL, SC	48 (100) 0	53.1 (mean)	45 (94)	38 months (median)	Pruritus reduction; VAS; 5-D itch scale	UDCA
Corpechot 2018 [39]	Bezafibrate vs placebo	RCT, DB, PG, PC, MC	100 (100) 0	53 (mean)	95 (95)	24 months	VAS; fatigue	UDCA
Lemoinne 2018 [46]	Fibrate (bezafibrate and fenofibrate)	Retrospective, MC	0 (0) 20 (100)	43.8 (median)	5 (25)	4.1 years (median)	NRS; pruritus reduction	UDCA
de Vries 2019 [68]	Bezafibrate vs placebo	RCT, DB, PC, PG, MC	26 (35.1) 46 (62.1)	46 (median, bezafibrate group) 50 (median, placebo group)	45 (60.8)	3 weeks	Pruritus reduction	UDCA, bile acid sequestrants
IBAT inhibitors (n = 3)								
Hegade 2017 [23]	Linerixibat vs placebo	RCT, DB, CO, PC, MC	22 (100) 0	52.9 (mean)	19 (86)	2 weeks	NRS; PBC-40/ PBC-27 itch; 5-D itch scale; interference of itch on sleep	UDCA
Al-Dury 2018 [21]	A4250/odevixibat	OL, SC	10 (100) 0	54.9 (mean)	9 (90)	4 weeks	PBC-40/ PBC-27 itch	UDCA
Mayo 2019 [24]	Maralixibat vs placebo	RCT, DB, PG, PC, MC	66 (100) 0	53.1 (mean)	60 (92.0)	13 weeks	Itch RO; PBC-40/PBC-27 itch; 5-D itch scale; interference of itch on sleep	UDCA
Other (n = 8)								
Bloomer 1975 [38]	Phenobarbital	Prospective, OL	7 (77.8) 2 (22.2)	32.3 (for $n = 15$) (average)	10 (66.7)	1–5 months	NRS	Cholestyramine
Turner 1990 [60]	Flumecinol vs placebo	RCT, DB, PG, PC	38 (92.7) NR	NR	NR	3 weeks	VAS	Cholestyramine
Turner 1994 (LD) [61]	Flumecinol vs placebo	RCT, DB, PG, PC	46 (92) NR	NR	47 (94)	3 weeks	Pruritus reduction; VAS	Antipruritic medication
Turner 1994 (HD) [61]	Flumecinol vs placebo	RCT, DB, PG, PC	19 (100) 0	NR	NR	3 weeks	Pruritus reduction; VAS	Cholestyramine
Villamil 2005 [63]	Lidocaine vs placebo	RCT, DB, PG, PC, SC	13 (72.2) 4 (22.2)	46.5 (mean)	14 (77.8)	7 days	VAS; fatigue	UDCA
O'Donohue 2005 [52]	Ondansetron vs placebo	RCT, DB, PG, PC	17 (89.5) 0 (0)	55.1 (mean)	16 (84.2)	5 days	Pruritus reduction; VAS; scratching activity	No anti-pruritics, no UDCA

Table 1 (continued)

Study	Interventions	Study design	PBC, N (%) PSC, N (%)	Age, years	Female gender, *n* (%)	Treatment duration	Main efficacy endpoint	Concomitant medications
Mayo 2018 [50]	NGM282 vs placebo	RCT, DB, PG, PC, MC	45 (100) 0	56.2 (mean)	41 (91.1)	28 days	Pruritus reduction; VAS; 5-D itch scale	UDCA
Mayo 2019 [51]	NGM282 vs placebo	RCT, DB, PG, PC, MC	0 (0) 62 (100)	NR	NR	12 weeks	NRS; 5-D itch scale	NR

CO, crossover; DB, double-blind; DEAE, diethylaminoethyl; IBAT, ileal bile acid transporter; MC, multicentre; N/A, not applicable; NR, not reported; NRS, numerical rating scale; OL, open-label; PBC, primary biliary cholangitis; PC, placebo-controlled; PG, parallel group; PSC, primary sclerosing cholangitis; RCT, randomised controlled trial; SB, single blind; SC, single centre; UDCA, ursodeoxycholic acid; VAS, visual analogue scale

data. Among the studies that did report these data, most reported zero or low rates of withdrawal for lack of efficacy; there were no reports of excoriations leading to withdrawal in these studies.

Pruritus Efficacy Outcomes

An overview of all pruritus efficacy outcomes reported in the included clinical studies is provided in Table 4 and Supplementary Table 4 provided in Online Resource 1.

Anion-Exchange Resins

Eight studies of anion-exchange resins were identified (Table 1). Cholestyramine was the most assessed intervention among the anion-exchange resins, with five studies evaluating a total of 56 treated patients with PBC (Table 3). Significant improvements in pruritus efficacy with cholestyramine were demonstrated in three of the five studies, two of which were RCTs that were both assessed as having a high risk of bias in at least one domain (Table 2). In one of the RCTs reported by Zuin and colleagues ($n=30$), cholestyramine significantly reduced pruritus NRS versus diethylaminoethyl (DEAE)-dextran ($P<0.001$), with resolution achieved in 45.5% of patients treated with cholestyramine compared with 36.8% of patients receiving DEAE-dextran [67]. In the Duncan study ($n=8$), a pruritus NRS assessed cumulative scores for the last 10 days of each treatment period; mean cumulative scores were significantly lower with cholestyramine (12.9) and terfenadine (15.8) compared with placebo (20.3) ($P<0.05$) and chlorpheniramine (19.3) [41].

Antibiotics

Eight studies of antibiotics were identified (Table 1). Among these, rifampicin was the most assessed intervention, with seven studies (three RCTs) including 110 treated patients with PBC (Table 3); an additional study reported by Ataei and colleagues also assessed rifampicin in comparison to the SSRI, sertraline (Table 1; [34]). Among these nine studies, one study ($n=16$) reported resolution of pruritus with rifampicin for all 10 patients who completed 12 months of treatment using a pruritus NRS. In another study that included 105 patients, only 17 (16.2%) patients reported resolution of pruritus. Four studies reported some beneficial effects of rifampicin on pruritus; however, data from these studies cannot be used as conclusive evidence for efficacy because of the limited sample size ($n=7$—22) and short duration of studies (≤ 2 weeks). In the open-label phase of the study by Podesta and colleagues, complete relief of pruritus symptoms was reported in 17/18 patients and partial relief in 1/18 patients within a few weeks of rifampicin

Table 2 Risk of bias within individual studies (randomised studies only) using the Cochrane risk of bias tool

Study	Interventions	Selection bias	Performance bias	Attrition bias	Detection bias	Reporting bias
Anion-exchange resins (RCTs: n=5/8)						
Duncan 1984 [41]	Cholestyramine vs terfenadine vs chlorpheniramine vs placebo	Unclear	Low	Unclear	High	Low
Floreani 1988 [42]	DEAE-dextran vs placebo	Unclear	Unclear	Unclear	Unclear	Unclear
Zuin 1991 [67]	Cholestyramine vs DEAE-dextran	Unclear	High	High	High	Low
Yokomori 2001 [15]	Colestilan vs no treatment	High	High	Unclear	High	Low
Kuiper 2010 [45]	Colesevelam vs placebo	Low	Low	Low	Low	Low
Antibiotics (RCTs: n=3/8)						
Ghent 1988 [43]	Rifampicin vs placebo	Low	Low	Low	Low	Low
Bachs 1989 [35]	Rifampicin vs phenobarbitone	Unclear	High	Unclear	High	Low
Podesta 1991 [53]	Rifampicin vs placebo	Low	Unclear	Low	Unclear	Low
Oral opiate agents (RCTs: n=3/7)						
Summerfield 1980 [55]	Naloxone vs placebo	Unclear	Unclear	Low	Low	Low
Wolfhagen 1997 [65]	Naltrexone vs placebo	Low	Low	Low	Unclear	Low
Terg 2002 [58]	Naltrexone vs placebo	Low	Low	Low	Unclear	Low
Selective serotonin reuptake inhibitors (RCTs: n=2/2)						
Mayo 2007 [49]	Sertraline vs placebo	Unclear	Unclear	Low	Unclear	Low
Ataei 2019 [34]	Sertraline vs rifampicin	High	Low	Low	Low	High
Fibrates (RCTs: n=3/6)						
Kanda 2003 [44]	Bezafibrate vs no treatment	Low	Low	Low	Low	Low
Corpechot 2018 [39]	Bezafibrate vs placebo	Low	Low	Low	Low	Low
de Vries 2019 [68]	Bezafibrate vs placebo	Low	Low	Unclear	Low	Unclear
IBAT inhibitors (RCTs: n=2/3)						
Hegade 2017 [23]	Linerixibat vs placebo	Low	Low	Low	Low	Low
Mayo 2019 [51]	Maralixibat vs placebo	Low	Low	Low	Low	Low
Other (RCTs: n=7/8)						
Turner 1990 [60]	Flumecinol vs placebo	Unclear	Unclear	Unclear	Unclear	Unclear
Turner 1994 (LD) [61]	Flumecinol vs placebo	Unclear	Low	Low	Low	Low
Turner 1994 (HD) [61]	Flumecinol vs placebo	Unclear	Low	Low	Low	Low
Villamil 2005 [63]	Lidocaine vs placebo	Low	Low	Low	Low	Unclear
O'Donohue 2005 [52]	Ondansetron vs placebo	Low	Low	Low	Low	Low
Mayo 2018 [50]	NGM282 vs placebo	Low	Low	Low	Low	Low
Mayo 2019 [51]	NGM282 vs placebo	Unclear	Unclear	Unclear	Unclear	Unclear

DEAE diethylaminoethy, *HD* high dose, *IBAT* ileal bile acid transporter, *LD* low dose, *RCT* randomised controlled trial

treatment, which was maintained over 8 months (Table 3; [53]).

Oral Opiate Agents

Seven studies of oral opiate agents were identified, three with naltrexone (two RCTs) and two with naloxone (one RCT) (Tables 1 and 3). Two studies ($n=20$ and $n=16$) showed a significant reduction in day- and night-time pruritus at the end of naltrexone treatment. In the open-label phase of the naltrexone study by Terg and colleagues, 5/7 patients retained a sustained response for the duration of the additional 2-month period with the remaining 2 patients experiencing an exacerbation of pruritus [58]. The

Table 3 Studies and pruritus efficacy measures by medication

Class	Intervention	N studies (*n* RCT)	N patients treated (*n* PBC)	Pruritus efficacy assessment (N studies)							
				NRS	Pruritus reduction	VAS	PBC-40 / 27 itch	5-D itch scale	Scratching activity	Sleep interference	N studies with any significant improvement[1] (RCTs)
Anion-exchange resins	Cholestyramine[2]	5 (2)	59 (56)	3	3	1					3 (2)
	Colesevelam[2]	1 (1)	17 (4)		1	1					
	Colestilan	1 (1)	5 (5)	1							1 (1)
	DEAE-Dextran	2 (1)	31 (31)	1	2						1 (1)
Antibiotics	Rifampicin[2]	7 (4[3])	191 (110)	2	4	3					4 (4)
	Rifaximin	1 (0)	16 (0)					1			
Opiate agents	Naloxone[2]	2 (1)	28 (> 8)			2			2		
	Naltrexone[2]	3 (2[3])	28 (23)		1	2				1	2 (2)
	Nalmefene[2]	1 (0)	9 (9)			1					1 (0)
	Nalfurafine[4]	1 (0)	44 (44)			1	1				1 (0)
Selective serotonin reuptake inhibitors	Sertraline[1]	2 (2)	30 (16)		1	2				1	1 (1)
Fibrates	Bezafibrate	5 (3)	167 (120)	1	3	2		1			3 (3)
	Fenofibrate	2 (0)	40 (20)	1	2						1 (0)
IBAT inhibitors	Maralixibat	1 (1)	42 (42)	1			1	1		1	
	Linerixibat	1 (1)	21 (21)	1			1	1		1	1 (1)
	A4250/odevixibat	1 (0)	10 (10)				1				
Other	Lidocaine	1 (1)	12 (9)			1					1 (1)
	Terfenadine	1 (1)	8 (7)	1							1 (1)
	Phenobarbital[1]	2 (1)	31 (29)	2	1						
	NGM282	2 (2)	72 (30)	1	1	1		2			
	Flumecinol	3 (3)	55 (> 51)		2	3					2 (2)
	Ondansetron	1 (1)	9 (> 7)		1	1			1		
	Chlorpheniramine	1 (1)	8 (7)	1							

[1]Studies reporting significant improvement in pruritus as defined by the authors of the studies; values in parentheses represent number of RCTs. Blank cells reflect significantly worse, not significant, or not reported

[2]Recommended treatment included in AASLD guidelines [14]

[3]One RCT includes an open-label extension reported in the same publication and not counted as a separate study

[4]A large Phase 3 trial was not included as it did not meet the 75% PBC/PSC inclusion criteria ($n = 90/317$)

> implies that the number was reported as total and not by study arm and/or studies did not report number of PBC patients

NOTE: table reports available data on all treatments; therefore, the same study may be included more than once

The number of patients refers to the number of patients treated with the specified medication

AASLD American Association for the Study of Liver Diseases, *DEAE* diethylaminoethyl, *NRS* numerical rating scale, *PBC* primary biliary cholangitis, *RCT* randomised controlled trial, *VAS* visual analogue scale

Table 4 Overview of pruritus efficacy measures and outcomes of included clinical trials

Study	Interventions	Pruritus efficacy assessment(s)	Timepoint of assessment	Key efficacy findings
Anion-exchange resins ($n=8$)				
Datta 1966 [40]	Cholestyramine	Pruritus reduction	13.2 months (mean)	Relieved, n = 14/20; partial relief, n = 3/20; no relief, n = 4/20
Van Berge Henegouwen 1974 [62]	Cholestyramine	NRS (0–3) Pruritus reduction	5 weeks	Mean (SD) reduction in NRS: -1.71 (0.49) No pruritus, n = 7/8; pruritus intensity reduced, n = 1/8
Duncan 1984 [41]	Cholestyramine Terfenadine Chlorpheniramine Placebo	NRS (0–3)	2 weeks	Mean (SD) difference from placebo in NRS: cholestyramine, -7.38 (7.21); terfenadine, -4.50 (4.31); chlorpheniramine, -1.00 (5.04)
Floreani 1988 [42]	DEAE-Dextran Placebo	Pruritus reduction	15 days	DEAE-Dextran: no pruritus, n = 5/12; decrease, n = 2/12; no change, n = 5/12; placebo: no change, n = 12/12
Zuin 1991 [67]	Cholestyramine DEAE-Dextran	NRS (0–3) Pruritus reduction	2 months	Mean NRS: cholestyramine, 0.99 ($P<0.01$); DEAE-Dextran, 1.04 ($P<0.01$) No pruritus: cholestyramine, n = 5/11; DEAE-Dextran, n = 7/19
Taha 1994 [57]	Cholestyramine UDCA Cholestyramine + UDCA No treatment	VAS (0–100)	2 weeks	Median (IQR) VAS: cholestyramine, 18.43 (5.84, 40.85); UDCA, 28.97 (14.99, 50.13); cholestyramine + UDCA, 27.81 (16.73, 51.86); no treatment, 33.27 (21.56, 75.08)
Yokomori 2001 [15]	UDCA Colestilan + UDCA	NRS (0–10)	4 weeks	Mean (SEM) NRS: UDCA, 2.5 (0.3) (NS vs baseline); colestilan + UDCA, 1.2 (0.2) ($P<0.05$ vs baseline)
Kuiper 2010 [45]	Colesevelam Placebo	VAS (0–100)	3 weeks	≥ 40% reduction in VAS: colesevelam, n = 6/17; placebo, n = 6/18
Antibiotics ($n=8$)				
Ghent 1988 [43]	Rifampicin Placebo	VAS (0–100)	2 weeks	Mean (SD) VAS: rifampicin, 176.5454 (52.4262); placebo, 346.0124 (97.2144)
Bachs 1989 [35]	Rifampicin Phenobarbitone	NRS (0–3) Pruritus reduction	2 weeks	Mean (SD) change from baseline in VAS: rifampicin, -1.57 (0.81); phenobarbitone, -0.33 (0.69) Pruritus improved: rifampicin, n = 19/21; phenobarbitone, n = 8/18

Table 4 (continued)

Study	Interventions	Pruritus efficacy assessment(s)	Timepoint of assessment	Key efficacy findings
Podesta 1991 [53]	Rifampicin Placebo	VAS (0–100) Pruritus reduction	1 week	Mean (SD) change in VAS: rifampicin, -65.93 (23.08); placebo, 16.43 (33.71) Full response (pruritus disappeared): rifampicin, n = 11/14; placebo, n = 0/14 Partial response (50% reduction): rifampicin, n = 3/14; placebo, n = 2/14
Podesta 1991 [53]	Rifampicin	Pruritus reduction	8.2 months (mean)	Full response (pruritus disappeared): n = 17/18 Partial response (50% reduction): n = 1/18
Bachs 1992 [36]	Rifampicin	NRS (0–3)	Multiple timepoints (2 weeks – 24 months)	Mean (SE) NRS (all assessments $P < 0.001$ vs baseline) Week 2, 0.6 (0.1); Month 3, 0.2 (0.1); Month 6, 0.4 (0.2); Month 9, 0.3 (0.1); Month 12, 0 (0); Month 15, 0 (0); Month 18, 0 (0); Month 24, 0 (0)
Loginov 1993 [48]	Rifampicin	Assessment not reported	2 weeks	Complete resolution, n = 4/7; significant decrease, n = 3/7
Tabibian 2017 [56]	Rifaximin	5-D itch scale	12 weeks	Median (IQR): 7 (6–8)
Webb 2018 [64]	Rifampicin	Pruritus reduction	N/A	Pruritus resolution: n = 17/105
Oral opiate agents ($n = 7$)				
Summerfield 1980 [55]	Naloxone Placebo	VAS (0–10)	1 night	Change in mean VAS: naloxone, -0.95; placebo, 1.33
Thornton 1988 [59]	Nalmefene	VAS (0–10)	Multiple timepoints (1–6 months)	Mean (SD) VAS: Month 1, 0.5722 (0.8588); Month 3, 0.6474 (0.8247); Month 6, 0.4257 (0.6077)
Bergasa 1992 [37]	Naloxone	VAS (0–10); measured by scratching activity monitoring system (counts per time)	24 h	19.38% (68.53)
Wolfhagen 1997 [65]	Naltrexone Placebo	VAS (0–100)	4 weeks	Mean (SE) change in VAS: naltrexone, -37.3992 (6.6136) (daytime) and -29.9804 (10.6726) (night-time); placebo, 3.1033 (4.2705) (daytime) and 0.3433 (4.1284) (night-time)
Terg 2002 [58]	Naltrexone Placebo	VAS (0–10)	2 weeks	Mean (SD) VAS: naltrexone, 3.55 (2.39) (daytime) and 3.55 (2.42) (night-time); placebo, 5.34 (2.41) (daytime) and 5.19 (2.55) (night-time)
Terg 2002 [58]	Naltrexone	Ongoing response	NR	Sustained response: n = 5/7 Exacerbation of pruritus: n = 2/7
Yagi 2018 [66]	Nalfurafine	VAS (0–100) PBC-40/-27 itch domain	12 weeks	Mean (SD) VAS: 29.3 (24.64)

Table 4 (continued)

Study	Interventions	Pruritus efficacy assessment(s)	Timepoint of assessment	Key efficacy findings
Selective serotonin reuptake inhibitors ($n=2$)				
Mayo 2007 [49]	Sertraline Placebo	VAS (0–10) Pruritus reduction	6 weeks	Mean change in VAS: sertraline, -1.86; placebo, 0.38 ≥ 20% reduction pruritus severity: sertraline, n = 8/12; placebo, n = 0/12
Ataei 2019 [34]	Sertraline Rifampicin	VAS (0–10)	4 weeks	Mean (SD) VAS: sertraline, 3.33 (1.68); rifampicin, 3.44 (2.749)
Fibrate ($n=6$)				
Kanda 2003 [44]	Bezafibrate No treatment	NR	NR	Pruritus decreased significantly in one patient taking UDCA plus bezafibrate 1 month after starting the trial
Levy 2011 [47]	Fenofibrate	Pruritus reduction	3 weeks	Improved, 28%; stable, 44%; deteriorated, 28%
Reig 2018 [54]	Bezafibrate No treatment	VAS (0–10) Pruritus reduction	38 months (median)	Median (IQR) VAS: bezafibrate, 0 (0. 1.4); no treatment, 4.6 (3.7, 6.5) Complete resolution, n = 16/26; partial resolution, n = 7/26; no change, n = 1/26 (for bezafibrate); NR (no treatment)
Corpechot 2018 [39]	Bezafibrate Placebo	VAS (0–10)	Multiple timepoints (3–24 months)	Median (IQR) VAS for bezafibrate vs placebo: Month 3: 0.0566 (0–2.9525) vs 2.7376 (0.2036–5.9502) Month 12: 0.0792 (0–1.9570) vs 2.3869 (0.0226–5.9502) Month 24: 0.0566 (0–1.4706) vs 2.3303 (0.9955–4.9434)
Lemoinne 2018 [46]	Fibrate: bezafibrate and fenofibrate	NRS (0–3) Pruritus reduction	1.56 years (median)	Improved, n = 7/8
de Vries 2019 [68]	Bezafibrate Placebo	VAS (0–10)	3 weeks	≥ 50% reduction in VAS: bezafibrate (45%) vs placebo (11%); P = 0.003

Table 4 (continued)

Study	Interventions	Pruritus efficacy assessment(s)	Timepoint of assessment	Key efficacy findings
IBAT inhibitors ($n=3$)				
Hegade 2017 [23]	Linerixibat Placebo	NRS (0–10) PBC-40/-27 itch domain 5-D itch scale	2 weeks	LS mean (SE) difference vs placebo in NRS: linerixibat 90 mg BID, 1.58 (0.450); linerixibat 90 mg BID – Sequence 1, 2.66 (0.7333); linerixibat 90 mg BID – Sequence 2, 1.58 (0.755); placebo – Sequence 1, 2.80 (0.733); placebo – Sequence 2, 4.60 (0.755) LS mean (SE) PBC-40/-27 itch domain score: linerixibat 90 mg BID, -0.59 (0.176); linerixibat 90 mg BID – Sequence 1, 2.73 (0.343); linerixibat 90 mg BID – Sequence 2, 1.99 (0.349); placebo – Sequence 1, 2.61 (0.343); placebo – Sequence 2, 3.29 (0.349) LS mean (SE) 5 D itch overall domain score: linerixibat 90 mg BID, -4.55 (1.030); linerixibat 90 mg BID – Sequence 1, 13.00 (1.342); linerixibat 90 mg BID – Sequence 2, 10.13 (1.388); placebo – Sequence 1, 15.09 (1.342); placebo – Sequence 2, 17.13 (1.388)
Al-Dury 2018 [21]	A4250/odevixibat Cholestyramine or colestipol	PBC-40/-27 itch domain	4 weeks	Mean (SD) overall domain scores: A4250/odevixibat, 4.50 (2.38); cholestyramine or colestipol, 10.50 (3.32)
Mayo 2019 [24]	Maralixibat Placebo	Adult Itch RO PBC-40/-27 5-D itch scale	13 weeks	LS mean (95% CI) difference vs placebo in adult Itch RO score: maralixibat 10 mg, -0.3 (-2.0, 1.5); maralixibat 20 mg, -4.0 (-14.2, 6.2) Mean (SD) PBC-40/-27 scores: maralixibat 10 mg, 6.7 (2.92); maralixibat 20 mg, 6.3 (2.88); placebo. 7.2 (3.76) LS mean (95% CI) difference vs placebo in 5-D itch scale score: maralixibat 10 mg, -0.5 (-3.4, 2.3); maralixibat 20 mg, -0.4 (-3.2, 2.5)
Other ($n=8$)				
Bloomer 1975 [38]	Phenobarbital	NRS (0–3)	2.86 months (mean)	Mean (SD) change from baseline in VAS: -1.11 (0.78)
Turner 1990 [60]	Flumecinol Placebo	VAS (0–100)	3 weeks	Mean change from baseline in VAS: flumecinol, 30.7; placebo, 37.3 ($P=0.017$)
Turner 1994 (LD) [61]	Flumecinol Placebo	VAS (0–100)	3 weeks	Median (95% CI) difference vs placebo in VAS: -8.0 (-20.8, 2.1)
Turner 1994 (HD) [61]	Flumecinol Placebo	VAS (0–100)	3 weeks	Median (95% CI) difference vs placebo in VAS: -19.8 (-40.7, -3.3)
Villamil 2005 [63]	Lidocaine Placebo	VAS (0–100)	7 days	Mean (SD) VAS: lidocaine, 50.5 (24.5); placebo, 71.7 (8.9)

Table 4 (continued)

Study	Interventions	Pruritus efficacy assessment(s)	Timepoint of assessment	Key efficacy findings
O'Donohue 2005 [52]	Ondansetron Placebo	VAS (0–10) Pruritus reduction	5 days	Mean percentage reduction in VAS: ondansetron, 21%; placebo, 22% ≥ 50% reduction in VAS: ondansetron, n = 1/9; placebo, n = 2/10
Mayo 2018 [50]	NGM282 vs Placebo	VAS (0–10)	4 weeks	LS mean (95%) change in VAS score vs placebo: -4.5 (-13.2, 4.3) Improved (≤ 20% from baseline): NGM282, 3/7; placebo, 3/10 No change: NGM282, 2/7; placebo, 5/10 Worsened (≥ 20% from baseline): NGM282, 0/7; placebo, 1/10
Mayo 2019 [51]	NGM282 Placebo	NRS (0–10)	12 weeks	Mean (95%) difference vs placebo in NRS: NGM282 1 mg, -0.47 (-1.93, 0.99); NGM282 3 mg, -0.52 (-1.96, 0.92)

BID twice daily, *CI* confidence interval, *CO* crossover, *DB* double blind, *IBAT* ileal bile acid transporter, *IQR* interquartile range, *LS* least squares, *MC* multicentre, *NR* not reported, *NRS* numerical rating scale, *OL* open label, *PBC* primary biliary cholangitis, *PC* placebo controlled; *PG* parallel group, *PSC* primary sclerosing cholangitis, *RCT* randomised controlled trial, *RO* reported outcome, *SB* single blind, *SC* single centre, *SD* standard deviation, *SE* standard error, *SEM* standard error of the mean, *UDCA* ursodeoxycholic acid, *VAS* visual analogue scale

twownaloxone studies ($n=8$ and $n=20$) showed a reduction in values on the scratching activity index; however, these studies cannot be used to support efficacy of naloxone as they observed patients for only 24 h and a single night, respectively (Table 4; Supplementary Table 4 provided in Online Resource 1).

Selective Serotonin Reuptake Inhibitors

Two studies of SSRIs were identified both of which were RCTs that evaluated sertraline (Table 1). One of the studies ($n=22$) showed improvements in pruritus and improvements in VAS scores with sertraline compared with placebo over 6 weeks, while the other study ($n=36$) showed improvements in VAS scores over 4 weeks in patients with PBC and PSC (Table 4; Supplementary Table 4 provided in Online Resource 1).

Fibrates

Six studies of fibrates were identified (Table 1). Bezafibrate was the most assessed intervention among the fibrates, with five studies (three RCTs) including 120 treated patients with PBC (Table 3). One study ($n=22$) reported a significant reduction in pruritus in 1 patient taking UDCA plus bezafibrate 1 month after starting the trial. Another study ($n=48$) reported complete disappearance of pruritus in 16 patients who reported pruritus prior to initiating bezafibrate therapy. Another study ($n=100$) reported improvements in pruritus VAS in patients assigned to bezafibrate compared with placebo over 24 months. In the study reported by de Vries and colleagues ($n=72$), bezafibrate treatment led to a significant reduction in VAS scores ($\geq 50\%$ reduction of pruritus) in patients with PBC and PSC compared with placebo (45% vs 11%; $P=0.003$) after 3 weeks of treatment (Table 4; Supplementary Table 4 provided in Online Resource 1; [68]).

IBAT Inhibitors

Three studies of IBAT inhibitors involving 73 treated patients with PBC were identified: one study (RCT) with linerixibat, one (RCT) with maralixibat and one with odevixibat. Linerixibat was shown to be significantly more effective than placebo in improving itch intensity based on PBC-40, PBC-27 and 5-D itch scale scores. Maralixibat significantly decreased weekly scores on the adult itch reported outcomes tool from baseline to Week 13; however, these reductions, as well as the reductions on the 5-D itch scale, were not significantly different compared with placebo. All 9 patients treated with odevixibat showed an improvement in pruritus based on 5-D itch, VAS and PBC-40 pruritus scores; however, this study was terminated following a high incidence of abdominal AEs.

HRQoL and PROs

The most commonly used PRO among the identified studies was the PBC-40 instrument, yet this was still only applied in 4/42 studies, and generally only in more recent studies [23, 50, 51, 66]. Hegade and colleagues reported a significantly greater reduction following linerixibat treatment compared with placebo in the itch and fatigue domains of PBC-40 [23]. In a Phase 2 study, no clinically meaningful improvements were observed with maralixibat compared with placebo on any domain of the PBC-40 [24]. In another Phase 2 study, treatment with NGM282 did not provide any significant changes in HRQoL assessed by the PBC-40 questionnaire [50]. Another study reported a significant reduction from baseline in the PBC-40 itch domain at Week 12 following nalfurafine treatment [66].

Other PROs assessed included the 36-Item Short Form survey (SF-36) in 2/42 studies [56, 66]. One of these studies reported non-significant reductions ranging from 2 to 20% across all SF-36 domains, except "role-physical" where no change was recorded after 12 weeks of rifaximin treatment [56]. The other study also did not show any significant changes in all domains of the SF-36 following nalfurafine treatment for 12 weeks [66].

Patient impression of change and patient global therapeutic benefit was recorded in only one of the 42 studies (the Phase 2 study of maralixibat) with no significant difference reported for either assessment for maralixibat versus placebo [24].

Satisfaction with study medication was assessed in 2/42 studies [43, 49]. In the study by Ghent and colleagues, 8/9 patients who completed the study reportedly preferred rifampicin to placebo [43]. In the study of Mayo and colleagues, all 12 patients reported a preference for sertraline, and chose to continue participating in an optional 2-year open-label long-term follow-up study [49].

Safety Outcomes

A total of 13 of the 42 studies identified reported treatment-emergent AEs, seven studies reported treatment-related AEs, ten studies reported serious AEs, and approximately a fifth (19%) reported treatment-related serious AEs (Supplementary Table 5 provided in Online Resource 1). Twenty-nine studies reported data relating to withdrawals. Four studies reported a $>40\%$ overall withdrawal rate, whereas nine studies reported no withdrawals in any treatment arm. Data related to withdrawals due to AEs was provided in 28 studies. Of these, two reported $>40\%$ withdrawal due to AEs, whereas nine studies reported no withdrawals due to AEs across all treatment arms.

Anion-Exchange Resins

AEs (occurring in ≥ 5% of patients) were reported in two of the eight studies of anion-exchange resins, both of which assessed cholestyramine. The most frequent reported AEs in patients treated with cholestyramine were diarrhoea (40 – 50%), vomiting (25%), constipation (6.7%) and abdominal pain (6.7%).

Antibiotics

AEs were reported in three of the seven rifampicin studies and the only study identified for rifaximin. The most commonly occurring AEs in patients treated with rifampicin were upper abdominal pain (28.6%), liver transplantation (18.8—20.0%), nausea (14.3%), leukocyte count decrease (14.3%), hepatitis/toxic hepatitis (4.8—12.5%) and peripheral oedema (6.3%).

Oral Opiate Agents

AEs were reported in two of the three studies identified for naltrexone. The most commonly occurring AEs in patients treated with naltrexone were dizziness (37.5—50.0%), opioid withdrawal like symptoms (50.0%), nausea (40.0—50%), vomiting (30.0%), abdominal cramps (25.0—62.5%) and hypertension (5.0%). AEs were not reported for naloxone, and the only study identified for nalmefene reported severe opioid withdrawal in 100% of patients, with increased bilirubin and deepening jaundice reported in 11% of patients.

Selective Serotonin Reuptake Inhibitors

AEs were reported in both studies identified for sertraline. The most commonly occurring AEs in patients were nausea (4.8—16.7%), insomnia (14.3%), fatigue (9.5%), liver transplantation (9.5%), increased bowel frequency (9.5%), visual hallucinations (9.5%) and dizziness (4.8%).

Fibrates

AEs were reported in two of the four studies identified for bezafibrate. The most commonly occurring AEs were myalgia (20.0%), nasopharyngitis (18.0%), abdominal pain (14.0%), arthralgia (14.0%), depressive mood (14.0%), flu-like syndrome (10.0%), polydipsia (9.1%), bronchitis (8.0%) and pruritus (8.0%).

IBAT Inhibitors

AEs were reported in two of the three studies included for IBAT inhibitors. The most commonly occurring AEs in patients treated with linerixibat were diarrhoea (33.0%), headache (29.0%), abdominal distention (14.0%) and abdominal pain (14.0%). The most commonly occurring AEs in patients treated with maralixibat were diarrhoea (52.4—70.0%), nausea (19.0—25.0%), upper abdominal pain (20.0—28.6%), abdominal pain (20.0—23.8%), abdominal distention (15.0%), fatigue (15%) and headache (9.5—15.0%).

Discussion

This systematic review of the literature clearly indicates that the evidence to support current treatment decisions for cholestatic pruritus in PBC and PSC is limited. Given that both are rare cholestatic liver diseases, and pruritus is recognised as a common and burdensome condition of both, patients with PBC and PSC were included in our review to ensure that all potentially informative studies were captured. Despite this approach, only a limited number of studies were identified, with the majority comprising small patient populations and were short in duration. Most studies, including those that assessed guideline-recommended treatments for pruritus, were also judged to be poor in quality. The double-blind RCT is considered to be the 'gold standard' method for conducting clinical research; however, only 25 of the 42 studies we identified were RCTs, with fewer than half ($n = 18$) double-blinded.

Nearly half of the identified studies were conducted more than two decades ago when the treatment paradigm for cholestatic pruritus was markedly different. Thus, findings from these earlier studies may no longer be relevant, owing to updates to clinical guidelines and changes in clinical practice. Social habits and patients' expectations have also evolved over time, which may have resulted in differences in patient experience and reporting of itch in more recent studies compared with the older investigations.

For pruritus efficacy measures, NRS, pruritus reduction/improvement and VAS were the most frequently reported endpoints; however, there were inconsistencies in the application of these measures between studies, including the use of different numerical scales, differences in the questions asked (e.g., itch intensity, worst itch, overall itch) and the time scale over which patients reported their symptoms (ranging from 12 h to 1 week). This variability in application of itch assessments measures highlights a clear need to establish and adopt universally accepted/gold standard methods in future studies.

Although cholestyramine is recommended as first-line treatment for moderate-severe pruritus associated with PBC and PSC [3, 13, 14], supportive evidence for its use appears limited, owing to a lack of RCTs, small sample sizes, absence of placebo arms, and short treatment duration. Furthermore, evidence to support the use of other treatment

classes for cholestatic pruritus is also limited. Antihistamines are commonly prescribed for treatment of pruritus, with the TARGET-PBC study reporting that 73% of patients were prescribed antihistamines for mild itch [4]. Despite the widespread use of antihistamines, this analysis identified only one study that met the criteria for inclusion in this systematic literature review and which concluded that antihistamines were not effective at treating pruritus. Inconsistency between study designs and outcome reporting makes comparisons of efficacy between the different treatment classes problematic and precludes robust statistical analysis. Given the wide variation in reporting standards for several efficacy outcomes and lack of formal statistical analysis to demonstrate differences between treatment arms, there is a clear need for improved study designs to provide quality evidence that can be incorporated into clinical guidelines and to assist physicians when considering the relative benefits and risks of currently available and future treatment options.

Our findings are in agreement with another recently published systemic review and meta-analysis assessing the efficacy of treatments for cholestatic pruritus [69]. The authors of this analysis also concluded that treatments for cholestatic pruritus are supported by data of very low quality and also noted a high degree of inconsistency in treatment approaches across studies. The authors identified a total of 93 studies, while we included 42 studies. This difference can be explained by the broader inclusion criteria in the published review, which included all cholestatic itch conditions, and not limited to PBC and PSC, as was the case in our analysis. Nevertheless, the findings of the reported analysis are consistent with our findings and provide further support for the need for more effective treatment options with good quality supportive evidence to manage this bothersome condition.

With respect to HRQoL and PROs, the paucity of reporting and lack of consistency in applied endpoints across studies that we observed is also consistent with another recent review of the PBC and PSC literature [70], which observed that only 60% of PRO concepts were measured with a PRO instrument, mostly a non-validated VAS or NRS. Development of only 3/83 PRO instruments was based on feedback from the target populations, and psychometric testing was limited to just 6 instruments [70]. For the PBC-40 instrument, significant reductions versus placebo were demonstrated only in the itch and fatigue domains following linerixibat treatment [23]; other studies either did not compare against placebo [66], or failed to show any significant difference between active treatment and placebo arms [24, 50]. It is possible that PRO reporting using PBC-40 is more likely in industry-sponsored research, or that use of this independent, well-validated and robust PRO measure may become more common in future studies.

In addition, to the aforementioned limitations, we noted a substantial risk of bias in many of the identified studies, as assessed using tools consistent with PRISMA-P guidelines [71]. Additional limitations include the earlier access date for the WHO ICTRP database in comparison to the other databases, and exclusion of studies with mixed cholestatic pruritus populations (which led to the exclusion of a large Phase 3 trial of nalfurafine).

With respect to safety, currently available therapies are either not well-tolerated (e.g., cholestyramine) or may be contraindicated in patients with liver disease (e.g., rifampicin). We noted a lack of consistency in defining and/or reporting AEs, particularly in older studies and a substantial variation in withdrawals and withdrawals due to AEs was observed between studies.

In summary, there is a paucity of evidence from high-quality trials for the treatment of pruritus in patients with PBC and PSC. While the primary objective of this systematic literature review was to evaluate evidence of efficacy of treatments for cholestatic pruritus associated with PBC and PSC, no strong evidence base could be identified because of various limitations of the evaluated studies. Owing to the limited data in the literature, there is a clear lack of understanding on the impact and burden of pruritus on patients with PBC and PSC. Additionally, our findings highlight an unmet need for a gold standard assessment for measuring and assessing itch. The lack of consistent and reproducible evidence available on efficacy, safety and impact on HRQoL of different treatments makes it difficult to interpret the relative benefit of currently recommended therapies, leaving physicians to rely on their clinical experience and trial-and-error, rather than evidence-based medicine. Consequently, patients suffering from this burdensome condition may need to suffer for longer duration to gain relief, considering the trial-and-error approach being used to treat pruritus rather than robust clinical evidence.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10620-023-07862-z.

Acknowledgments Editorial support (in the form of writing assistance, including preparation of the draft manuscript under the direction and guidance of the authors, collating and incorporating author comments for each draft, assembling tables and figures, grammatical editing and referencing) was provided by Hayley Butler, PhD, at Fishawack Indicia Ltd, part of Fishawack Health, and was funded by GSK.

Author contributions HTS was involved in study design and data analysis/interpretation. ARdS, AHT and MMM were involved in data analysis/interpretation. JJD, JAM and JVC were involved in study design, study execution and data analysis/interpretation. All authors reviewed and edited the manuscript and approved the final version.

Funding This study (Study 209985) was funded by GSK.

Data availability Not applicable as this study does not include individual patient data.

Declarations

Conflict of interest HTS, ARdS and MMM are employees of GSK and hold stocks/shares in the company. AHT was an employee of GSK at

the time of the study and holds GSK stocks/shares. JAM is an employee of Medical Decision Modelling Inc., which is a health economic firm commissioned by GSK to conduct this research. JJD and JVC were employees of Medical Decision Modelling Inc. at the time of the study.

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