Bijlage Evidence tabellen en GRADE profielen

Evidence tabellen en GRADE profielen behorende bij de uitgangsvragen die via de GRADE methodiek zijn uitgewerkt.

Onderzoeksvraag 1: lokale medicamenteuze behandeling

Wat is het effect van lokale medicamenteuze behandeling op jeuk bij patiënten in de palliatieve fase?
What is the effect of local pharmacological treatment on pruritus in patients in the palliative phase?

Patients	patients in the palliative phase with pruritus (with the exception of pruritus due to primary dermatological conditions and pruritus due to kidney failure)
Intervention	local pharmacological treatment
Comparator	other pharmacological treatment, placebo, no treatment
Outcome	Critical: pruritus (NRS, VAS), quality of life, patient satisfaction Important: adverse events, depression

Evidence tables

Systematic reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Andrade 2020	• Design: systematic review + meta-analysis • Funding: Instituto Universitario Hospital Italiano (IUHI), Argentina, Dermatology Department, Argentina, National Institute for Health Research (NIHR), UK; CoI: none • Search date: Jul 2019 • Databases: Cochrane Skin Group Specialised Register, CENTRAL, MEDLINE, Embase, and trials registries • Study designs: (quasi)RCTs	• Eligibility criteria: participants of any age (adults and children), of either sex, with a diagnosis of chronic pruritus of unknown origin	Topical and systemic pharmacological interventions Non-pharmacological interventions	CRITICAL OUTCOMES • Pruritus (NRS, VAS): not reported • Quality of life: not reported • Patient satisfaction: not reported IMPORTANT OUTCOMES • Adverse events: not reported • Depression: not reported	Level of evidence: - • Review process in duplicate, no restrictions • Included relevant RCT: none

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• N included studies: N=1				

Primary studies

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Ibrahim 2017	• Design: CCT • Funding: not reported; CoI: not reported • Setting: single university centre, Egypt • Sample size: N=50 • Duration: 2 weeks; Jun 2014 – Jun 2016	• Eligibility criteria: patients suffering from chronic pruritus, that is, hepatic, renal, and diabetic pruritus • *A priori* patient characteristics: ○ Mean age: 51.8y ○ Female: 48% ○ Hepatic 30%, diabetic 32%	Topical crude clove oil 10% in petrolatum (N=25) vs. Topical petrolatum (N=25)	CRITICAL OUTCOMES • Pruritus (NRS, VAS): 5-D itch scale ○ Mean duration: -0.92 vs. -0.12 h/d, p=0.001 ○ Mean degree: -2.00 vs. -0.48, p=0.000 ○ Mean direction: -1.72 vs. -0.28, p=0.000 ○ Mean disability: -3.04 vs. -0.44, p=0.0001 ○ Mean distribution: -2.42 vs. -0.24, p=0.0001 ○ Mean total 5-D score: -9.84 vs. -1.56, p=0.000001 • Quality of life: not reported • Patient satisfaction: not reported IMPORTANT OUTCOMES • Adverse events: not reported • Depression: not reported	Level of evidence: high risk of bias • No randomization • Unclear blinding

Abbreviations: 95%CI: 95% confidence interval; CCT: controlled clinical trial; CoI: conflict of interest; NRS: numeric rating scale; RCT: randomised controlled trial; VAS: visual analogue scale.

GRADE profiles

Topical clove oil

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Topical clove oil**	**Placebo oil**	**Relative (95%CI)**	**Absolute**		
Pruritus: 5-D itch scale												
1	CCT	Very serious	No serious inconsistency	No serious indirectness	No serious imprecision	None	25	25	-	-9.84 vs. -1.56 p=0.000001	VERY LOW	CRITICAL
Quality of life												
0	No evidence from RCTs											
Patient satisfaction												
0	No evidence from RCTs											

Adverse events	
0	No evidence from RCTs
Depression	
0	No evidence from RCTs

[1] No randomization, unclear blinding.

References

1. Andrade A, et al. Interventions for chronic pruritus of unknown origin. Cochrane Database Syst Rev. 2020 Jan 25;1(1):CD013128.
2. Ibrahim, I.M., et al., Effectiveness of topical clove oil on symptomatic treatment of chronic pruritus. Journal of Cosmetic Dermatology. 2017;16(4):508-11.

Onderzoeksvraag 2: systemische medicamenteuze behandeling
Wat is het effect van systemische medicamenteuze behandeling op jeuk bij patiënten in de palliatieve fase?
What is the effect of systemic pharmacological treatment on pruritus in patients in the palliative phase?

Patients	patients with pruritus in the palliative phase (with the exception of pruritus due to primary dermatological conditions and pruritus due to kidney failure)
Intervention	pharmacological treatment
Comparator	other pharmacological treatment, placebo, no treatment
Outcome	Critical: pruritus (NRS, VAS), quality of life, patient satisfaction Important: adverse events, depression

Evidence tables

Systematic reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Andrade 2020	• Design: systematic review + meta-analysis • Funding: Instituto Universitario Hospital Italiano (IUHI), Argentina, Dermatology Department, Argentina, National Institute for Health Research (NIHR), UK; CoI: none • Search date: Jul 2019 • Databases: Cochrane Skin Group Specialised Register, CENTRAL, MEDLINE, Embase, and trials registries • Study designs: (quasi)RCTs • N included studies: N=1	• Eligibility criteria: participants of any age (adults and children), of either sex, with a diagnosis of chronic pruritus of unknown origin	Topical and systemic pharmacological interventions Non-pharmacological interventions	CRITICAL OUTCOMES • Pruritus (NRS, VAS): 5 mg Serlopitant (vs. placebo) ○ VAS at 6w: RR 2.06, 95%CI 1.27-3.35; mean % decrease: MD -14.20, 95%CI -26.63 to -1.77 ○ VAS at 10w: mean % decrease: MD -11.70, 95%CI -23.06 to -0.34 ○ NRS at 6w: RR 2.07, 95%CI 1.21-3.53; mean % decrease: MD -10.30, 95%CI -20.01 to -0.59 1 mg Serlopitant (vs. placebo) ○ VAS at 6w: RR 1.50, 95%CI 0.89-2.54; mean % decrease: MD -13.10, 95%CI -24.38 to -1.82 ○ VAS at 10w: mean % decrease: MD -10.50, 95%CI -21.73 to 0.73 ○ NRS at 6w: RR 1.43, 95%CI 0.79-2.57; mean % decrease: MD -10.70, 95%CI -20.41 to -0.99 0.25 mg Serlopitant (vs. placebo)	Level of evidence: low risk of bias • Review process in duplicate, no restrictions • Included RCT: Yosipovitch 2018 (Serlopitant vs. placebo); 55% of the patients had chronic pruritus of unknown origin

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
				○ VAS at 6w: RR 1.66, 95%CI 1.00-2.77; mean % decrease: MD -5.80, 95%CI -17.16 to 5.56 ○ VAS at 10w: mean % decrease: MD -7.40, 95%CI -18.63 to 3.83 ○ NRS at 6w: RR 1.69, 95%CI 0.96-2.95; mean % decrease: MD -7.10, 95%CI -16.80 to 2.60 • Quality of life: <u>5 mg Serlopitant (vs. placebo)</u> ○ DLQI at 6w: MD -4.20, 95%CI -11.68 to 3.28 ○ DLQI at 10w: MD -4.00, 95%CI -11.48 to 3.48 <u>1 mg Serlopitant (vs. placebo)</u> ○ DLQI at 6w: MD -6.90, 95%CI -14.38 to 0.58 ○ DLQI at 10w: MD -2.30, 95%CI -9.78 to 5.18 <u>0.25 mg Serlopitant (vs. placebo)</u> ○ DLQI at 6w: MD -5.70, 95%CI -13.18 to 1.78 ○ DLQI at 10w: MD -4.40, 95%CI -11.88 to 3.08 • Patient satisfaction: not reported IMPORTANT OUTCOMES • Adverse events at 6w: <u>5 mg Serlopitant (vs. placebo)</u> ○ RR 1.48, 95%CI 0.87-2.50 ○ Most commonly reported: somnolence (N=3), diarrhoea (N=2), headache (N=1), upper respiratory tract infection (N=1), and urinary tract infection (N=2) <u>1 mg Serlopitant (vs. placebo)</u> ○ RR 1.45, 95%CI 0.86-2.47 ○ Most commonly reported: somnolence (N=3), diarrhoea (N=4), headache (N=3), nasopharyngitis (N=3), pruritus (N=2), nausea (N=2), dry mouth (N=2), and musculoskeletal pain (N=2) <u>0.25 mg Serlopitant (vs. placebo)</u> ○ RR 1.29, 95%CI 0.75-2.24	

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
				○ Most commonly reported: somnolence (N=1), headache (N=1), nasopharyngitis (N=2), upper respiratory tract infection (N=3), pruritus (N=2), and arthralgia (N=2) • Depression: not reported	
Khurana 2006	• Design: systematic review + meta-analysis • Funding: not reported; CoI: not reported • Search date: 2004 • Databases: Medline, PreMedline, CDSR, ACP Journal Club, DARE, CENTRAL, Embase • Study designs: prospective comparative trials • N included studies: N=5 RCTs (61 patients)	• Eligibility criteria: patients with pruritus associated with chronic cholestasis	Rifampin	CRITICAL OUTCOMES • Pruritus (NRS, VAS): resolution of pruritus ○ Fixed-effect: OR 15.2 (95%CI 5.2-45.6, p=0.001) ○ Random effect: OR 20.1 (95%CI 3.9-103; p=0.001) • Quality of life: not reported • Patient satisfaction: not reported IMPORTANT OUTCOMES • Adverse events: nausea and decreased appetite in 2 patients, 1 patients with allergic reaction, 1 patient with haemolytic anemia • Depression: not reported	Level of evidence: high risk of bias • Language restriction unclear • Selection and quality appraisal in duplicate; unclear for data extraction • Included RCTs: Ghent 1988, Bachs 1989, Woolf 1990, Cynamon 1990, Podesta 1991
Pongcharoen 2016	• Design: systematic review + meta-analysis • Funding: none; CoI: one reviewer with several conflicts • Search date: Mar 2015 • Databases: PubMed, Embase, Cochrane Library • Study designs: placebo-controlled RCTs • N included studies: N=26, of which 9 with cholestatic patients	• Eligibility criteria: studies that evaluated the effect of a systemic treatment on itch • Exclusion: acute and chronic urticaria; analgesics; immunosuppressive agents; disease-modifying drugs	Systemic treatments	See Siemens 2016: no additional studies in comparison with that review	Level of evidence: variable (depending on treatment) • Limited to English studies • Unclear if review process was done in duplicate • No formal quality appraisal • Included (relevant) RCTs: Zylicz 2003, Terg 2002, Wolfhagen 1997, O'Donohue 2005, Mayo 2007, Bergasa 2006, Ghent 1988, Podesta 1991, Kuiper 2010
Siemens 2016	• Design: systematic review + meta-analysis • Funding: German Ministry for Education and Research (BMBF),	• Eligibility criteria: patients 18+, suffering from pruritus combined with an incurable advanced malignant or non-malignant disease	Pharmaceutical interventions	CRITICAL OUTCOMES • Pruritus (NRS, VAS): ○ Paroxetine (1 study, N=26): MD (NAS) after 1w -0.78 points (95%CI -1.19 to -0.37) ○ Sertraline (1 study, N=12): MD (VAS) 2.24 cm, p=0.009	Level of evidence: variable (depending on treatment) • No language restriction • Review process in duplicate

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	Grant No. 01KG0819; CoI: none • Search date: Jun 2016 • Databases: Medline, Embase, CENTRAL (Aug 2012 also: Cochrane Library, BIOSIS previews, CINAHL, PsycInfo); trial registers, experts • Study designs: RCTs • N included studies: N=50, of which 16 relevant to the question			○ Naltrexone (2 studies, N=36): MD (VAS) -2.26 cm (95%CI -3.19 to -1.33) ○ Ondansetron (1 study, N=19): mean pruritus perception over 5d -21% vs. -22% ○ Gabapentin (1 study, N=16): no significant difference ○ Rifampicin (3 studies, N=45): pruritus improvement SMD -1.73 (95%CI -2.45 to -1.02) ○ Cholestyramine (1 study, N=8): positive effects ○ Colesevelam (1 study, N=38): VAS day score p=1.00, VAS night score p=0.74 ○ Flumecinol (2 studies, N=69): improvement yes/no RR 1.89 (95%CI 1.05-3.39) ○ Propofol (1 study, N=10): decrease of pruritus of at least 4 points on verbal rating scale: 85% vs. 10%, p<0.01 ○ Lidocaine (1 study, N=18): VAS day 2 39.1 vs. 70.8 mm; VAS day 3 48.7 vs. 72.0 mm; p<0.05 ○ Hydroxyzine hydrochloride, pentoxifylline, triamcinolone, indomethacin (1 study, N=40): median improvement on 4-point pruritus scale 2.0 vs. 2.0 vs. 2.5 vs. 1.0 • Quality of life: ○ Colesevelam (1 study, N=38): SF-36, no significant difference; physical functioning p=0.67, role physical functioning p=0.50, bodily pain p=1.00, general health p=0.48, vitality p=0.90, social functioning p=0.37, emotional functioning p=0.17 or mental health p=0.26 ○ Flumecinol (2 studies, N=69): difference in median improvement: study 1: 5.0 mm (95%CI 0.4-13.0; p=0.02); study 2: 3.5 mm (95%CI -5.9 to 24.9) • Patient satisfaction: ○ Paroxetine (1 study, N=26): MD -1.08 (95%CI -1.98 to -0.18)	• Included (relevant) studies: Zylicz 2003, Terg 2002, Wolfhagen 1997, O'Donohue 2005, Mayo 2007, Bergasa 2006, Ghent 1988, Bachs 1989, Podesta 1991, Duncan 1984, Kuiper 2010, Turner 1994a, Turner 1994b, Borgeat 1993, Vilamil 2005, Smith 1997

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
				IMPORTANT OUTCOMES • Adverse events: ○ Paroxetine (1 study, N=26): 2 withdrawals because of nausea and vomiting; nausea MD -0.46 (-0.87 to -0.05; p=0.04); vomiting MD 0.18 (-0.08 to 0.43; p=0.184); sleepiness MD -0.70 (-0.18 to -1.22) ○ Sertraline (1 study, N=12): at least one event: 11 vs. 8 ○ Naltrexone (1 study, N=20): risk for at least one adverse event RR 2.67 (95%CI 1.32-5.39) ○ Ondansetron (1 study, N=19): risk for at least one adverse event RR 0.89 (95%CI 0.34-2.32) ○ Gabapentin (1 study, N=16): at least one event: 5 vs. 2 ○ Cholestyramine (1 study, N=8): diarrhoea and vomiting in 4 patients ○ Colesevelam (1 study, N=38): mild stool changes 1 vs. 4 ○ Flumecinol (2 studies, N=69): no adverse events ○ Propofol (1 study, N=10): at least one event: 5 vs. 0 ○ Lidocaine (1 study, N=18): mild tinnitus in 2 patients ○ Hydroxyzine hydrochloride, pentoxifylline, triamcinolone, indomethacin (1 study, N=40): at least one event: 9 vs. 2 vs. 1 vs. 6 • Depression: ○ Gabapentin (1 study, N=16): no comparison provided ○ Sertraline (1 study, N=12): no comparison provided	
To 2012	• Design: systematic review • Funding: not reported; CoI: none	• Eligibility criteria: patients with cholestatic or uremic pruritus	Ondansetron	CRITICAL OUTCOMES • Pruritus (NRS, VAS): ○ Muller 1998: composite peak VAS score -1.34, 95%CI -2.56 to -0.12, p=0.033	Level of evidence: high risk of bias • English studies only

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Search date: Oct 2008 • Databases: Medline, Embase, CINAHL • Study designs: placebo-controlled RCTs • N included studies: N=5, of which 3 with cholestatic patients (N=50)			○ O'Donohue 2005: mean reduction in VAS over 5d 21% vs. 22%, NS ○ Jones 2007: improvement of 0.21 points in mean NRS-assessed pruritus • Quality of life: not reported • Patient satisfaction: not reported IMPORTANT OUTCOMES • Adverse events: ○ O'Donohue 2005: constipation 44% vs. 0%, p=0.03; nausea 0 vs. 3; headache 0 vs. 2 ○ Jones 2007: constipation N=10, abdominal cramps N=6, nausea N=3, headache N=3, dizziness N=2 • Depression: not reported	• Duplicate selection and quality appraisal, unclear for data extraction • Jadad-score used, individual quality items not reported • Included studies: Muller 1998, O'Donohue 2005, Jones 2007

Primary studies

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Ataei 2019	• Design: RCT • Funding: funded by a grant from Hamadan University of Medical Sciences; CoI: none • Setting: single centre, Iran • Sample size: N=36 • Duration: unclear, follow-up of 1 month	• Eligibility criteria: patients with established primary biliary cirrhosis or primary sclerosing cholangitis, and moderate to severe pruritus • *A priori* patient characteristics: ○ Mean age: 38 vs. 45.2y • Female: 39 vs. 50%	Sertraline 100 mg/d (N=18) vs. Rifampin 300 mg/d (N=18)	CRITICAL OUTCOMES • Pruritus (NRS, VAS): ○ VAS (SEM): sertraline baseline 6.17 (1.47), at 4w 3.33 (1.68); rifampin baseline 6.06 (1.55), at 4w 3.44 (2.75); p=0.74 • Quality of life: not reported • Patient satisfaction: not reported IMPORTANT OUTCOMES • Adverse events: mild nausea in first 2 weeks: 3 vs. 1; no treatment interruption Depression: not reported	Level of evidence: high risk of bias • Permuted block randomisation • Randomisation with 36 pieces of paper, half on them written A and half B Single blinded
Bergasa 1992	• Design: cross-over placebo-controlled study • Funding: US government; CoI: not reported • Setting: unclear, US • Sample size: N=8 • Duration: unclear	• Eligibility criteria: patients with primary biliary cirrhosis and chronic pruritus • *A priori* patient characteristics: ○ Age: 40-66y ○ Female: 100%	Naloxone 0,2 μg/kg/min (N=8) vs. Placebo (N=8)	CRITICAL OUTCOMES • Pruritus (NRS, VAS): ○ VAS: no consistent change between mean values during naloxone infusions and corresponding values during placebo infusions • Quality of life: not reported • Patient satisfaction: not reported	Level of evidence: high risk of bias • Randomisation and allocation concealment is not mentioned, and probably not done • No blinding of clinicians • No statistical comparison

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
				IMPORTANT OUTCOMES • Adverse events: no significant untoward clinical developments occurred during the infusions • Depression: not reported	
Bergasa 1995	• Design: cross-over RCT • Funding: National Institutes of Health; CoI: not reported • Setting: clinical research referral center • Sample size: N=29 • Duration: 4 days	• Eligibility criteria: patients with pruritus and cholestasis associated with cholestatic liver disease or advanced chronic hepatocellular disease • *A priori* patient characteristics: ○ Age: 11-68y ○ Female: 22/29	Naloxone 0,2 µg/kg/min for 48h (N=29) vs. Placebo (N=29)	CRITICAL OUTCOMES • Pruritus (NRS, VAS): MD -0.582 (95%CI -0.988 to -0.176; p<0.01) • Quality of life: not reported • Patient satisfaction: not reported IMPORTANT OUTCOMES • Adverse events: anxiety in 4 patients; non-specific symptoms 34% vs. 24% • Depression: not reported	Level of evidence: high risk of bias • Balanced randomisation with code • Unclear allocation concealment • Double-blinded • Statistician was unblinded
Bergasa 1999	• Design: RCT • Funding: not reported; CoI: not reported • Setting: tertiary referral centre, the Netherlands • Sample size: N=11 • Duration: 2 months	• Eligibility criteria: adult patients with unrelieved incapacitating generalized pruritus, complicating well-characterized stable chronic liver disease • *A priori* patient characteristics: not reported	Nalmefene: dose gradually increased from 2x2 mg/d to 2x20 mg/d vs. Placebo	CRITICAL OUTCOMES • Pruritus (NRS, VAS): overall mean decrease during nalmefene = 77%, no comparison with placebo • Quality of life: not reported • Patient satisfaction: not reported IMPORTANT OUTCOMES • Adverse events: no serious adverse events; 1 patient with generalized discomfort, chest tightness, and lack of appetite; 1 patient with insomnia and joint stiffness associated with low-grade fever, peripheral blood eosinophilia; 6/8 patients with mild opiate withdrawal-like reaction • Depression: not reported	Level of evidence: high risk of bias • Randomisation method and allocation concealment unclear • Double blind • Data on 8 patients who had baseline measurements taken and who had received at least 1 course of nalmefene were available for analysis; 3 patients not included in analysis • Partly cross-over: 4 of the analysed patients did not receive placebo
Di Padova 1984	• Design: RCT • Funding: not reported; CoI: not reported • Setting: single university centre, Italy • Sample size: N=10 • Duration: 4 weeks	• Eligibility criteria: patients aged 16+ suffering from intra- and extrahepatic cholestasis in the absence of complete obstruction of extrahepatic bile ducts, and with serum bilirubin concentrations less than 8 mg/dl • *A priori* patient characteristics:	Microporous Cholestyramine 3x3 g/d (N=5) vs. Placebo (N=5)	CRITICAL OUTCOMES • Pruritus (NRS, VAS): reduction in VAS score: ○ After 2w: -55.7% vs. +8.2%, p<0.05 ○ After 4w: -63.6% vs. +24.7%, p<0.05 • Quality of life: not reported • Patient satisfaction: not reported IMPORTANT OUTCOMES	Level of evidence: high risk of bias • Randomisation method and allocation concealment unclear • Double blind

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		○ Mean age: 61.2 vs. 40.4y, p<0.05 ○ Female: 50%		• Adverse events: ○ None of the patients discontinued therapy ○ 1 patient with melena under Cholestyramine, 1 patient with constipation under placebo • Depression: not reported	• Imbalanced baseline characteristics
Floreani 1988	• Design: cross-over RCT • Funding: not reported; CoI: not reported • Setting: single centre, Italy • Sample size: N=12 • Duration: unclear	• Eligibility criteria: female patients with primary biliary cirrhosis and severe pruritus • *A priori* patient characteristics: ○ Mean age: 50y ○ Female: 100%	Diethylaminoethyl-dextran 3x1g/d up to 3x2g/d (N=12) vs. Placebo (N=12)	CRITICAL OUTCOMES • Pruritus (NRS, VAS): 4-point scale; no improvement during placebo; 5 with complete disappearance during DEAE-dextran, and 2 improvement; no statistical comparison • Quality of life: not reported • Patient satisfaction: not reported IMPORTANT OUTCOMES • Adverse events: no side effects observed • Depression: not reported	Level of evidence: high risk of bias • Randomisation method and allocation concealment unclear • Double-blind • Selective outcome reporting (no statistical comparison)
Juby 1994	• Design: cross-over RCT • Funding: not reported; CoI: not reported • Setting: single university centre, UK • Sample size: N=5 • Duration: 7 days	• Eligibility criteria: patients with chronic liver disease and intense itching • *A priori* patient characteristics: not reported	Buprenorphine 2x200 µg/d for 3d (N=5) vs. Placebo (N=5)	CRITICAL OUTCOMES • Pruritus (NRS, VAS): 1 patient with improvement during buprenorphine, 1 patient with improvement during placebo; no statistical comparison • Quality of life: not reported • Patient satisfaction: not reported IMPORTANT OUTCOMES • Adverse events: nausea, fatigue, dizziness • Depression: not reported	Level of evidence: high risk of bias • Randomisation method and allocation concealment unclear • Double-blind • Selective outcome reporting (no statistical comparison)
Kumada 2017	• Design: RCT • Funding: financial support of Toray Industries; CoI: 2 employees of Toray Industries • Setting: multicentre study, Japan • Sample size: N=317 • Duration: 84 days; Dec 2010 – Nov 2012	• Eligibility criteria: patients aged 20+ with chronic liver disease and uncontrollable pruritus • *A priori* patient characteristics: ○ Mean age: 65.5y ○ Female: 57.4%	Nalfurafine hydrochloride 2.5 µg (N=105) vs. Nalfurafine hydrochloride 5 µg (N=109) vs.	CRITICAL OUTCOMES • Pruritus (NRS, VAS): change in VAS at 4w vs. placebo: ○ 2.5 µg: MD 9.31 (95%CI 2.94-15.69; p=0.0022) ○ 5 µg: MD 8.22 (95%CI 1.88-14.55; p=0.0056) • Quality of life: not reported • Patient satisfaction: not reported IMPORTANT OUTCOMES • Adverse events:	Level of evidence: high risk of bias • Randomisation: a designated person generated an assignment table in a permuted block design stratified by study site by using multiple block sizes • Double-blind • Blinding of outcome assessors unclear

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
			Placebo (N=103)	○ Discontinuation: 2.9% vs. 3.7% vs. 1.9% ○ Adverse drug reactions with an incidence of at least 5%: insomnia, somnolence, dizziness, constipation, pollakiuria, increased blood prolactin, increased blood antidiuretic hormone, increased blood thyroid stimulating hormone, increased total bile acids • Depression: not reported	• Industry-sponsored
McCormick 1994	• Design: RCT • Funding: grant from the North East Thames Regional Health Authority Locally Organised Research Scheme; CoI: not reported • Setting: single university centre, UK • Sample size: N=18 • Duration: 6 months	• Eligibility criteria: patients with primary biliary cirrhosis • *A priori* patient characteristics: ○ Mean age: 59 vs. 62y ○ Female: 100% vs. 50% ○ 3 patients received cholestyramine for pruritus; 13 in total had pruritus	Thalidomide 100 mg/d (N=10) vs. Placebo (N=8)	CRITICAL OUTCOMES • Pruritus (NRS, VAS): 4-point scale; thalidomide 5/7 improvement, placebo 3/6 improvement; no statistical comparison • Quality of life: not reported • Patient satisfaction: not reported IMPORTANT OUTCOMES • Adverse events: 2 withdrawals because of fatigue and general malaise; 2 extra patients with same symptoms; all 4 on Thalidomide • Depression: not reported	Level of evidence: high risk of bias • Randomisation method and allocation concealment unclear; no balanced randomisation with regards to pruritus • Double-blind • Blinding of assessors unclear • Selective outcome reporting (no statistical comparison) • Not taken into account that 3 patients received Cholestyramine
Schwörer 1995	• Design: cross-over placebo-controlled study • Funding: not reported; CoI: not reported • Setting: single university centre, Germany • Sample size: N=10 • Duration: unclear	• Eligibility criteria: patients with cholestatic liver disease and associated pruritus not improved with conventional antipruritic therapy • *A priori* patient characteristics: ○ Age: 37-66y ○ Female: 60%	Ondansetron (N=10) vs. Placebo (N=10)	CRITICAL OUTCOMES • Pruritus (NRS, VAS): effects of ondansetron (4 mg, 8 mg) on itch intensity were significantly different ($p<0.05$) from placebo response during the controlled observation period from 15 to 120 min • Quality of life: not reported • Patient satisfaction: not reported IMPORTANT OUTCOMES • Adverse events: no side effects during treatment with ondansetron or placebo • Depression: not reported	Level of evidence: high risk of bias • Randomisation and allocation concealment is not mentioned, and probably not done • No blinding of clinicians • No statistical comparison
Ständer 2009	• Design: quasi-RCT	• Eligibility criteria: patients with severe chronic pruritus	Paroxetine 20 mg/d (N=39)	CRITICAL OUTCOMES	Level of evidence: high risk of bias

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Funding: not reported; CoI: none • Setting: single university centre, Germany • Sample size: N=72 • Duration: unclear	• *A priori* patient characteristics: ○ Mean age: 59.2y ○ Female: 45/72 ○ Underlying disease in 20 patients, unclear in 52 patients	vs. Fluvoxamine 50 mg/d (N=33)	• Pruritus (NRS, VAS): mean VAS reduction 3.7 vs. 3.2, p=0.826 • Quality of life: not reported • Patient satisfaction: not reported IMPORTANT OUTCOMES • Adverse events: ○ 3 withdrawals, of which 2 because of side effects (hypertension, vertigo, fatigue) ○ Medication stopped: 10/39 vs. 8/33 ○ At least one adverse effect: 74.3% vs. 66.6% • Depression: not reported	• Patients alternately received one of two treatments • Open-label study

Abbreviations: 95%CI: 95% confidence interval; CCT: controlled clinical trial; CoI: conflict of interest; DLQI: Dermatology Life Quality Index; MD: mean difference; NAS: numeric analogue scale; NRS: numeric rating scale; OR: odds ratio; RCT: randomised controlled trial; RR: relative risk; SF-36: 36-item Short Form Survey; SMD: standardised mean difference; UK: United Kingdom; VAS: visual analogue scale.

GRADE profiles

Cholestatic prutitus

Cholestyramine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Cholestyramine**	**Placebo**	**Relative (95%CI)**	**Absolute**		
Pruritus: reduction in VAS												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[1]	None	5	5	-	After 2w: 55.7% vs. 8.2%, p<0.05 After 4w: 63.6% vs. 24.7%, p<0.05	VERY LOW	CRITICAL
Quality of life												
0	No evidence from RCTs											

Patient satisfaction											
0	No evidence from RCTs										
Adverse events: at least one event											
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[1]	None	5	5	-	1 vs. 1	VERY LOW	IMPORTANT
Depression											
0	No evidence from RCTs										

[1] Unclear randomization and allocation concealment, imbalanced baseline characteristics.

[2] No CI provided, precision unclear; small sample size.

Colesevalam

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colesevalam	Placebo	Relative (95%CI)	Absolute		
Pruritus: VAS, 40% reduction												
1	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	17	18	-	Day score: p=1.00 Night score: p=0.74	MODERATE	CRITICAL
Quality of life: SF-36												
1	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	17	18	-	Physical functioning p=0.67, role physical functioning p=0.50, bodily pain p=1.00, general health p=0.48, vitality p=0.90, social functioning p=0.37, emotional functioning p=0.17 or mental health p=0.26	MODERATE	CRITICAL
Patient satisfaction												
0	No evidence from RCTs											
Adverse events: minor stool changes												
1	RCT	No serious	No serious inconsistency	No serious indirectness	Very serious[2]	None	17	18	-	1 vs. 4	LOW	IMPORTANT

		risk of bias										
Depression												
0	No evidence from RCTs											

[1] No CI provided, precision unclear.

[2] No statistical comparison.

DEAE-Dextran

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**DEAE-Dextran**	**Placebo**	**Relative (95%CI)**	**Absolute**		
Pruritus: 4-point-scale, improvement or complete resolution												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	12	12	-	7 vs. 0	VERY LOW	CRITICAL
Quality of life												
0	No evidence from RCTs											
Patient satisfaction												
0	No evidence from RCTs											
Adverse events												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	12	12	-	0 vs. 0	VERY LOW	IMPORTANT
Depression												
0	No evidence from RCTs											

[1] Unclear randomization method and allocation concealmemt, unclear blinding of outcome assessors, selective outcome reporting.

[2] No statistical comparison; small sample size.

Flumecinol

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Flumecinol**	**Placebo**	**Relative (95%CI)**	**Absolute**		
Pruritus: improvement yes/no												
2	RCT	Serious[1]	Serious[2]	No serious indirectness	Serious[3]	None	34	35	RR 1.89 (1.05-3.39)	-	VERY LOW	CRITICAL
Quality of life: VAS, difference in median improvement												
2	RCT	Serious[1]	Serious[4]		Serious[5]	None	24	26	-	5.0 mm		CRITICAL

				No serious indirectness						(0.4-13.0)	VERY LOW	
							10	9	-	3.5 mm (-5.9 to 24.9)		
Patient satisfaction												
0	No evidence from RCTs											
Adverse events												
2	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[5]	None	34	35	-	0 vs. 0	LOW	IMPORTANT
Depression												
0	No evidence from RCTs											

[1] Unclear risk of bias: randomization method and allocation concealment not mentioned.

[2] I^2 59.23%.

[3] CI includes 1.25.

[4] Inconsistent results.

[5] No statistical comparison; small sample size.

Gabapentin

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Gabapentin**	**Placebo**	**Relative (95%CI)**	**Absolute**		
Pruritus: VAS												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	7	6	-	No significant difference	VERY LOW	CRITICAL
Quality of life												
0	No evidence from RCTs											
Patient satisfaction												
0	No evidence from RCTs											
Adverse events: at least one event												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	7	6	-	5 vs. 2	VERY LOW	IMPORTANT
Depression												
0	No evidence from RCTs											

[1] High risk of bias: unclear blinding of assessors, 3/16 patients excluded from analysis.

[2] No CI provided and/or no statistical comparison; small sample size.

Propofol

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Propofol	Placebo	Relative (95%CI)	Absolute		
Pruritus: VRS, decrease of at least 4 points												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	10	10	-	85% vs. 10% p<0.01	VERY LOW	CRITICAL
Quality of life												
0	No evidence from RCTs											
Patient satisfaction												
0	No evidence from RCTs											
Adverse events: at least one event												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	10	10	-	5 vs. 0	VERY LOW	IMPORTANT
Depression												
0	No evidence from RCTs											

[1] Poorly described study, unclear methods.

[2] No CI provided and/or no statistical comparison, small sample size.

Lidocaine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lidocaine	Placebo	Relative (95%CI)	Absolute		
Pruritus: mean VAS-score												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	11	5	-	Day 2: 39.1 vs. 70.8 mm Day 3: 48.7 vs. 72.0 mm p<0.05	LOW	CRITICAL
Quality of life												
0	No evidence from RCTs											
Patient satisfaction												
0	No evidence from RCTs											

Adverse events: mild tinnitus												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	11	5	-	2 vs. 0	LOW	IMPORTANT
Depression												
0	No evidence from RCTs											

[1] Unclear allocation concealment; selective reporting.

[2] No CI provided and/or no statistical comparison, small sample size.

Naltrexone

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Naltrexone**	**Placebo**	**Relative (95%CI)**	**Absolute**		
Pruritus: VAS												
2	RCT	No serious risk of bias	No serious inconsistency[1]	No serious indirectness	No serious imprecision	None	26	26	MD -2.24 (-3.19 to -1.33)	-	HIGH	CRITICAL
Quality of life												
0	No evidence or RCTs											
Patient satisfaction												
0	No evidence or RCTs											
Adverse events												
1	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	20	20	RR 2.67 (1.32-5.39)	-	HIGH	IMPORTANT
Depression												
0	No evidence or RCTs											

[1] I^2 55%, but on forest plot no visible inconsistency.

Naloxone

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Naloxone**	**Placebo**	**Relative (95%CI)**	**Absolute**		
Pruritus: VAS												

1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	29	29	MD -0.582 (-0.988 to -0.176)	-	LOW	CRITICAL
1	CCT	Very serious[3]	No serious inconsistency	No serious indirectness	Very serious[4]	None	8	8	No significant difference	-	VERY LOW	CRITICAL
Quality of life												
0	No evidence from RCTs											
Patient satisfaction												
0	No evidence from RCTs											
Adverse events: non-specific symptoms												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[4]	None	29	29	-	34% vs. 24%	LOW	IMPORTANT
Depression												
0	No evidence from RCTs											

[1] High risk of bias: unclear allocation concealment, statistician not blinded.

[2] Estimated SMD = -0.78, 95%CI -1.32 to -0.24, which includes -0.5.

[3] High risk of bias: not randomised, issues with blinding, selective outcome reporting.

[4] No CI reported and/ or no statistical comparison.

Nalfurafine

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Nalfurafine**	**Placebo**	**Relative (95%CI)**	**Absolute**		
Pruritus: VAS-score after 4w												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	2.5 µg: 105 5 µg: 109	103	-	2.5 µg: MD 9.31 (2.94-15.69) 5 µg: MD 8.22 (1.88-14.55)	LOW	CRITICAL
Quality of life												
0	No evidence from RCTs											
Patient satisfaction												
0	No evidence from RCTs											
Adverse events: insomnia												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	2.5 µg: 105 5 µg: 109	103	-	2.5 µg: 6 vs. 3 5 µg: 5 vs. 3	LOW	IMPORTANT

Adverse events: somnolence											
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	2.5 µg: 105 5 µg: 109	103	-	2.5 µg: 6 vs. 1 5 µg: 8 vs. 1	LOW	IMPORTANT
Adverse events: dizziness											
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	2.5 µg: 105 5 µg: 109	103	-	2.5 µg: 2 vs. 4 5 µg: 6 vs. 4	LOW	IMPORTANT
Adverse events: constipation											
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	2.5 µg: 105 5 µg: 109	103	-	2.5 µg: 4 vs. 2 5 µg: 8 vs. 2	LOW	IMPORTANT
Adverse events: pollakiuria											
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	2.5 µg: 105 5 µg: 109	103	-	2.5 µg: 6 vs. 1 5 µg: 8 vs. 1	LOW	IMPORTANT
Depression											
0	No evidence from RCTs										

[1] Possible issues with blinding; industry-sponsored.

[2] 2.5 µg: estimated SMD = 0.40, 95%CI 0.12-0.67, which includes 0.5. 5 µg: estimated SMD = 0.35; 95%BI 0.08-0.62, which includes 0.5.

[3] No CI provided and/or no statistical comparison.

Nalmefene

No formal comparison between Nalmefene and placebo, so no GRADEing possible.

Buprenorfine

No formal comparison between Buprenorphine and placebo, so no GRADEing possible.

Ondansetron

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ondansetron**	**Placebo**	**Relative (95%CI)**	**Absolute**		
Pruritus: VAS or NRS score												
3	RCT	Serious[1]	Serious[2]	No serious indirectness	Serious[3]	None	18	18	Composite peak VAS score -1.34, 95%CI -2.56 to -0.12, p=0.033	-	VERY LOW	CRITICAL

							8	10	-	VAS reduction over 5d: 21% vs. 22%, NS		
							14	14	-	Improvement of 0.21 points in mean NRS-assessed pruritus		
1	CCT	Very serious[4]	No serious inconsistency	No serious indirectness	Very serious[5]	None	10	10	-	Effects of ondansetron (4 mg, 8 mg) on itch intensity were significantly different ($p<0.05$) from placebo response during the controlled observation period from 15 to 120 min	VERY LOW	CRITICAL
Quality of life												
0	No evidence from RCTs											
Patient satisfaction												
0	No evidence from RCTs											
Adverse events: constipation												
1	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[5]	None	18	18	-	44% vs. 0% p=0.03	LOW	IMPORTANT
Depression												
0	No evidence from RCTs											

[1] High risk of bias: unclear randomization method in 2 studies, small sample sizes.

[2] Inconsistent results.

[3] No meta-analysis possible, but small sample sizes suggest lack of precision.

[4] No randomization or blinding.

[5] Insufficient data to estimate precision, small sample size.

Rifampicin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Rifampicin**	**Placebo**	**Relative (95%CI)**	**Absolute**		
Pruritus: cessation												
5	RCT	Serious[1]	No serious inconsistency[2]	No serious indirectness	No serious imprecision	None	61	61	OR 20.1 (3.9-103)	-	MODERATE	CRITICAL
Pruritus: improvement on different scales												
3	RCT	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	42	39	SMD -1.73 (-2.45 to -1.02)	-	MODERATE	CRITICAL
Quality of life												
0	No evidence from RCTs											
Patient satisfaction												
0	No evidence from RCTs											
Adverse events												
1	RCT	Very serious[3]	No serious inconsistency	No serious indirectness	Very serious[4]	None	21	18	RR 0.29 (0.03-2.51)	-	VERY LOW	IMPORTANT
Depression												
0	No evidence from RCTs											

[1] High risk of bias: issues with randomization and/or allocation concealment, 2 studies were not blinded.

[2] No heterogeneity, p=0.16.

[3] High risk of bias: issues with randomization and/or allocation concealment, not blinded.

[4] CI includes 0.75 and 1.25.

Sertraline

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sertraline**	**Placebo**	**Relative (95%CI)**	**Absolute**		
Pruritus: VAS												

1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	12	12	MD 2.24 p=0.009	-	LOW	CRITICAL
Quality of life												
0	No evidence from RCTs											
Patient satisfaction												
0	No evidence from RCTs											
Adverse events: at least one event												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[3]	None	12	12	-	11 vs.8	VERY LOW	IMPORTANT
Depression												
0	No evidence from RCTs											

[1] Unclear randomization, allocation concealment and blinding.

[2] No CI provided, small sample size.

[3] No statistical comparison, small sample size.

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sertraline**	**Rifampicin**	**Relative (95%CI)**	**Absolute**		
Pruritus: VAS												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	18	18	MD at 4w -0.11 p=0.74	-	VERY LOW	CRITICAL
Quality of life												
0	No evidence from RCTs											
Patient satisfaction												
0	No evidence from RCTs											
Adverse events: at least one event												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[3]	None	18	18	-	3 vs. 1	VERY LOW	IMPORTANT
Depression												
0	No evidence from RCTs											

[1] Insufficient allocation concealment, unclear blinding.

[2] Calculated SMD = -0.01, CI includes 0.5 at both sides.

[3] No statistical comparison, small sample size.

Thalidomide

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Thalidomide**	**Placebo**	**Relative (95%CI)**	**Absolute**		
Pruritus: 4-point scale												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	7	5	-	71% vs. 50%	VERY LOW	CRITICAL
Quality of life												
0	No evidence from RCTs											
Patient satisfaction												
0	No evidence from RCTs											
Adverse events												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	7	5	-	No statistical comparison	VERY LOW	IMPORTANT
Depression												
0	No evidence from RCTs											

[1] Issues with randomization, selective outcome reporting and statistical analysis.

[2] No statistical comparison, no CI. Small sample size.

Hiv patients

Indomethacin vs. Triamcolone lotion

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Indomethacin**	**Triamcolone lotion**	**Relative (95%CI)**	**Absolute**		
Pruritus: 4-point scale												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	10	10	-	-2.5 vs. 1.0 p<0.05	VERY LOW	CRITICAL
Quality of life												
0	No evidence from RCTs											
Patient satisfaction												
0	No evidence from RCTs											
Adverse events: at least one event												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	10	10	-	9 vs. 1	VERY LOW	IMPORTANT
Depression												

0	No evidence from RCTs

[1] Very unclear methods.

[2] No CI, small sample size.

Palliative patients

SSRI

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Paroxetine**	**Placebo**	**Relative (95%CI)**	**Absolute**		
Pruritus: NAS score after 1w												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	24	24	MD -0.78 (-1.19 to -0.37)	-	LOW	CRITICAL
Quality of life												
0	No evidence from RCTs											
Patient satisfaction												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	24	24	MD -1.08 (-1.98 to -0.18)	-	LOW	CRITICAL
Adverse events: nausea												
1	RCT	Very serious[3]	No serious inconsistency	No serious indirectness	Serious[2]	None	24	24	MD -0.46 (-0.87 to -0.05)	-	VERY LOW	IMPORTANT
Adverse events: sleepiness												
1	RCT	Very serious[3]	No serious inconsistency	No serious indirectness	Serious[2]	None	24	24	MD -0.70 (-1.22 to -0.18)	-	VERY LOW	IMPORTANT
Depression												
0	No evidence from RCTs											

[1] Unclear randomization, allocation concealment and blinding

[2] Wide CI including -1 (between 0 and -1 is considered not clinically meaningful).

[3] Two patients withdrew because of important nausea and vomiting.

Chronic pruritus of unknow origin

SSRI

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paroxetine	Fluvoxamine	Relative (95%CI)	Absolute		
Pruritus: mean VAS reduction												
1	RCT	Very serious[1]	No serious inconsistency	Serious[2]	Serious[3]	None	39	33	-	3.7 vs. 3.2 p=0.826	VERY LOW	CRITICAL
Quality of life												
0	No evidence from RCTs											
Patient satisfaction												
0	No evidence from RCTs											
Adverse events: at least one event												
1	RCT	Very serious[1]	No serious inconsistency	Serious[2]	Serious[3]	None	39	33	-	74.3% vs. 66.6%	VERY LOW	IMPORTANT
Depression												
0	No evidence from RCTs											

[1] Quasi-randomized, open-label.

[2] 20/72 patients had known origin.

[3] No CI provided.

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