

Itching (Pruritus) in Primary Biliary Cholangitis



PBCers Conference, Houston, Texas

May 19, 2018

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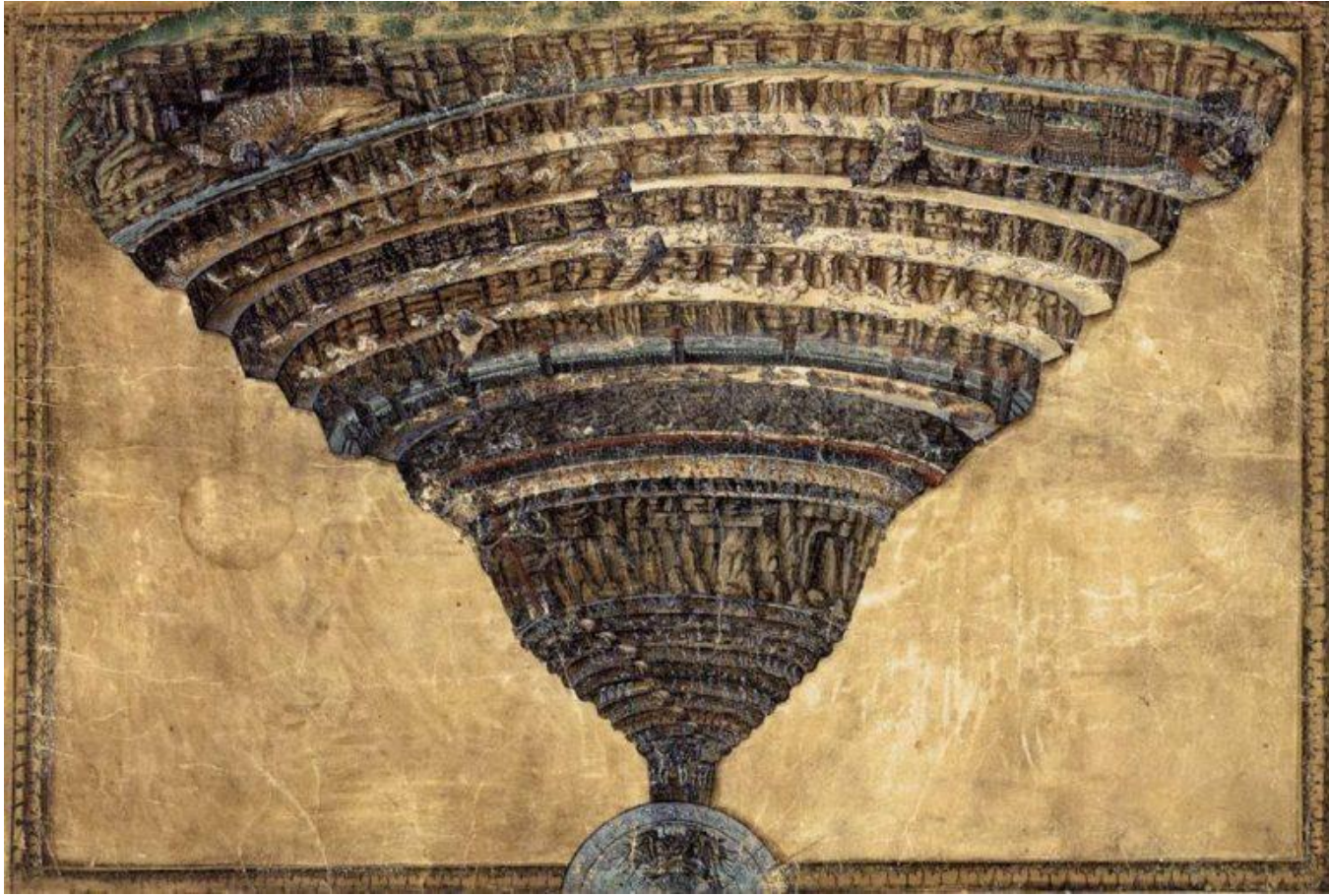
UT Southwestern Medical Center, Dallas, Texas

Itching in Primary Biliary Cholangitis.

- In urso trials, 60%-70% of patients had itching, 23% severe
- Not correlated with disease severity
- Not unique to PBC, but appears earlier in biliary diseases
- Localized-→ Generalized. Predilection for palms/soles
- No primary rash, but may have secondary skin lesions (scratches, red crusted bumps, darkening of skin, butterfly sparing).
- Worse in evenings
- Exacerbated by heat/pressure
- 74% disturbed sleep
- May cause social isolation, depression
- Intermittent, progressive, self-extinguishing



Dante's Inferno: Relentless Itching in Hell



Botticelli



8th Circle of Hell

Ways to Measure Itching

5-D Itch Scale

1. **Duration:** During the last 2 weeks, how many hours a day have you been itching?

Less than 6hrs/day 1 6-12 hrs/day 2 12-18 hrs/day 3 18-23 hrs/day 4 All day 5

2. **Degree:** Please rate the intensity of your itching over the past 2 weeks

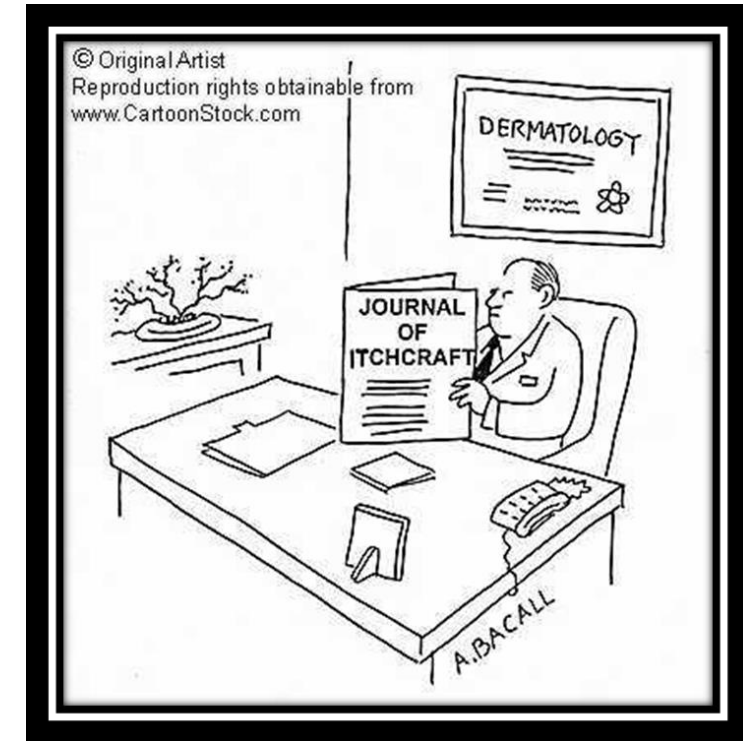
Not present 1 Mild 2 Moderate 3 Severe 4 Unbearable 5

3. **Direction:** Over the past 2 weeks has your itching gotten better or worse compared to the previous month?

Completely resolved 1 Much better, but still present 2 Little bit better, but still present 3 Unchanged 4 Getting worse 5

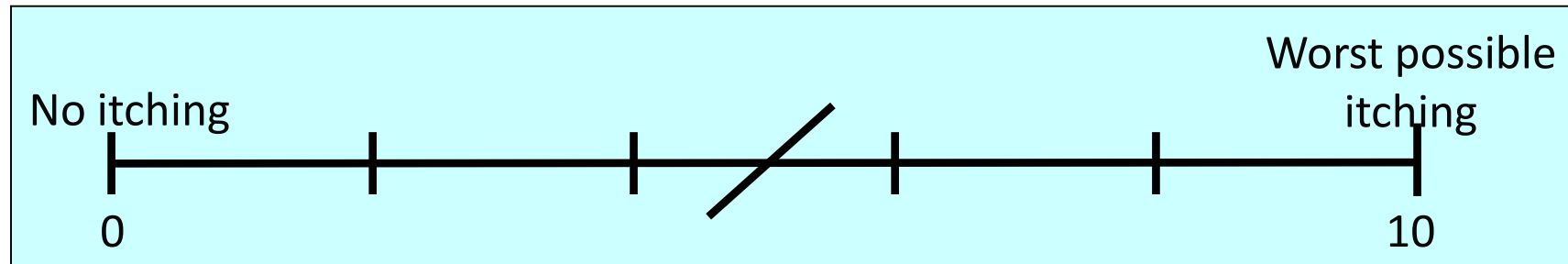
4. **Disability:** Rate the impact of your itching on the following activities over the last 2 weeks

	Never affects sleep <input type="checkbox"/> 1	Occasionally delays falling asleep <input type="checkbox"/> 2	Frequently delays falling asleep <input type="checkbox"/> 3	Delays falling asleep and occasionally wakes me up at night <input type="checkbox"/> 4	Delays falling asleep and frequently wakes me up at night <input type="checkbox"/> 5	
Sleep						
	N/A <input type="checkbox"/>	Never affects this activity <input type="checkbox"/> 1	Rarely affects this activity <input type="checkbox"/> 2	Occasionally affects this activity <input type="checkbox"/> 3	Frequently affects this activity <input type="checkbox"/> 4	Always affects this activity <input type="checkbox"/> 5
Leisure/Social						
Housework/Errands						
Work/School						



5. **Distribution:** Mark whether itching has been present in the following parts of your body over the last 2 weeks. If a body part is not listed, choose the one that is closest anatomically.

Head/Scalp <input type="checkbox"/>	Present <input type="checkbox"/>	Soles <input type="checkbox"/>	Present <input type="checkbox"/>
Face <input type="checkbox"/>		Palms <input type="checkbox"/>	
Chest <input type="checkbox"/>		Tops of Hands/Fingers <input type="checkbox"/>	
Abdomen <input type="checkbox"/>		Forearms <input type="checkbox"/>	
Back <input type="checkbox"/>		Upper Arms <input type="checkbox"/>	
Buttocks <input type="checkbox"/>		Points of Contact w/ Clothing (e.g waistband, undergarment) <input type="checkbox"/>	
Thighs <input type="checkbox"/>		Groin <input type="checkbox"/>	
Lower legs <input type="checkbox"/>			
Tops of Feet/Toes <input type="checkbox"/>			



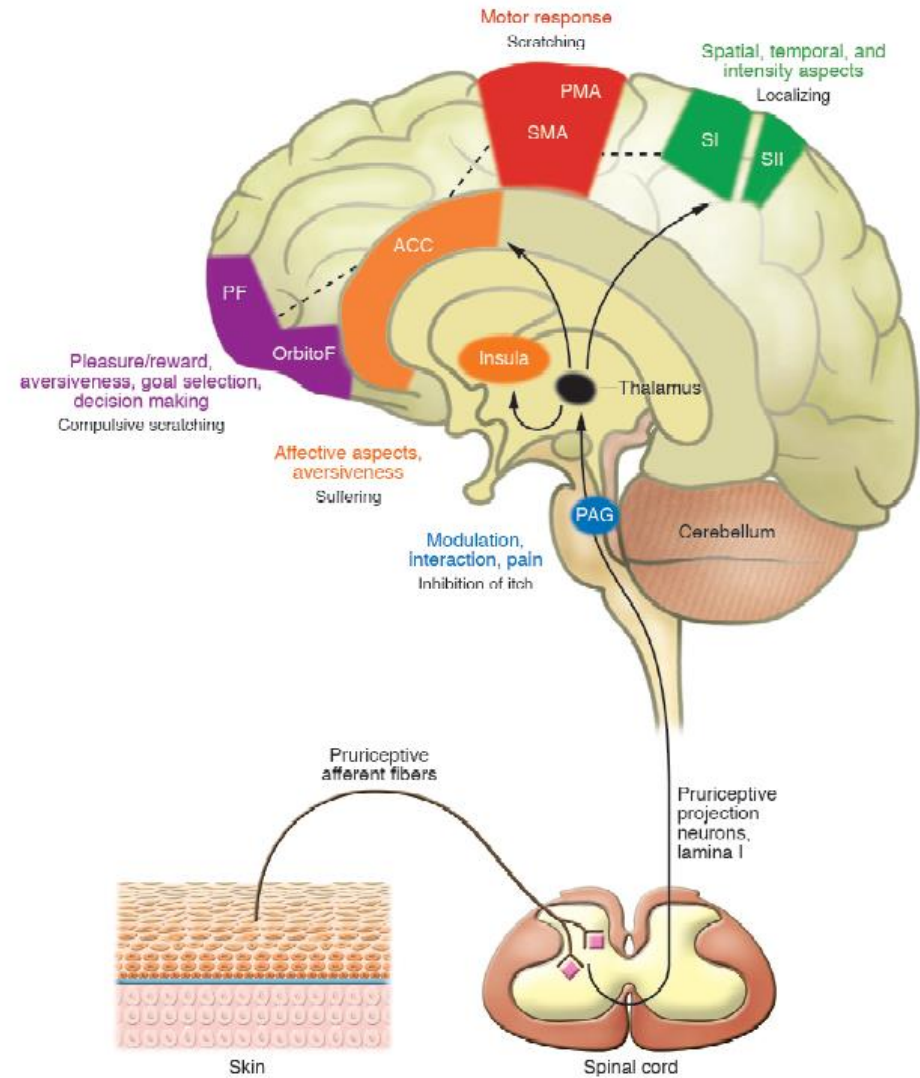
Liver doctors are not good at addressing itch

<u>Specialty</u>	<u># of Notes Documenting Pruitus</u>	
Burn	89/106	(84%)
Dermatology	91/92	(99%)
Liver	48/90	(53%)
Primary Care	17/24	(71%)
Emergency	5/15	(33%)
Surgery	2/10	(20%)
Psychiatry	2/6	(33%)
HIV	4/5	(80%)
Medicine	4/5	(80%)
Gynecology	2/3	(67%)
Other	2/11	(18%)
Total	266/373	(71%)

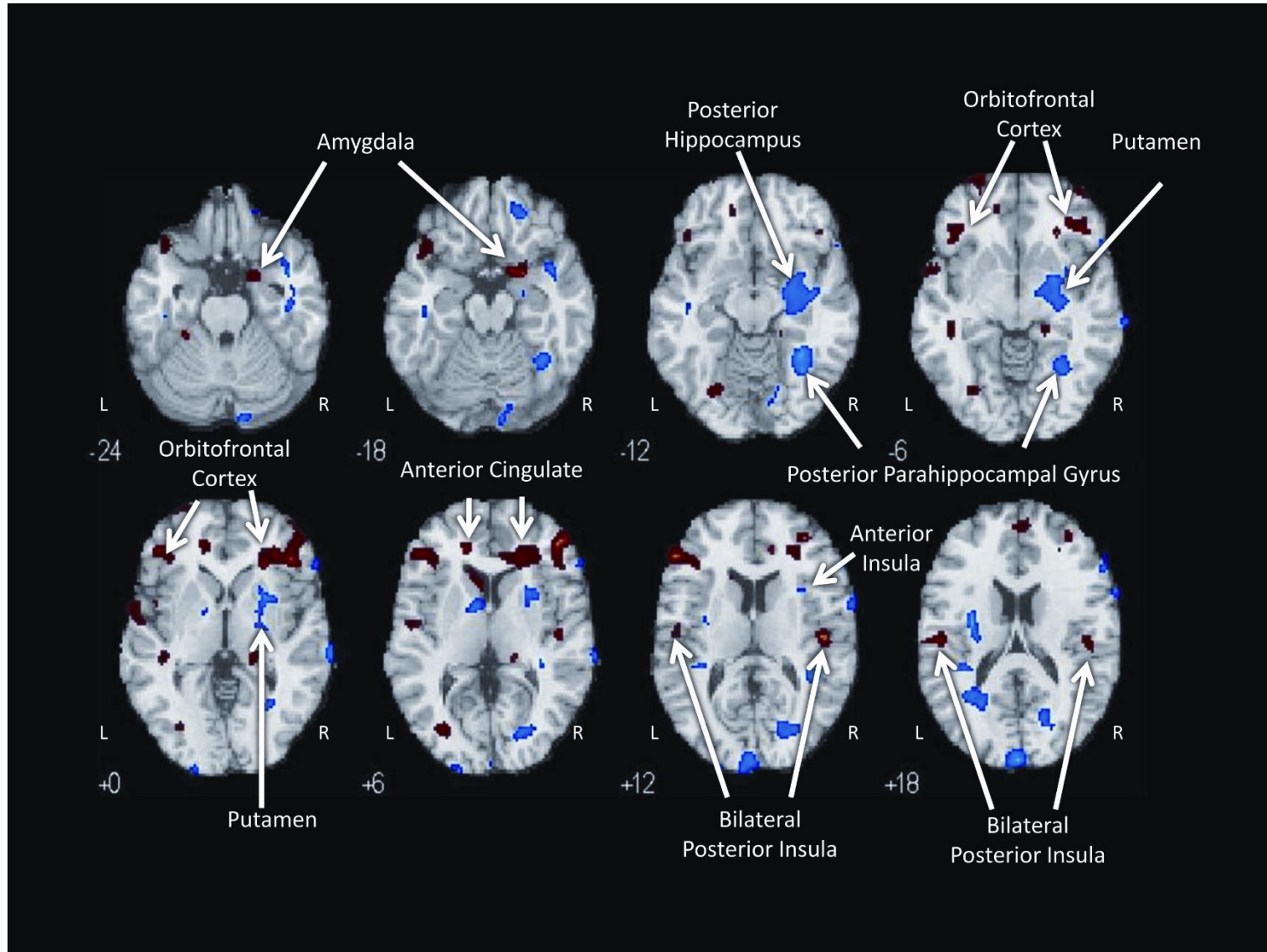
The Cause of Itch in PBC is Complex

Putative Culprits

- Histamine
- Opioids
- Bile Acids
- Sulfated Progesterones
- Prostaglandins
- Serotonin
- Acetylcholine
- IL-31
- Endocannabinoids
- Endothelins
- Endovanilloids
- Leukotrienes
- LPA/autotaxin



Activation of the Limbic System during Itch in Patients with PBC



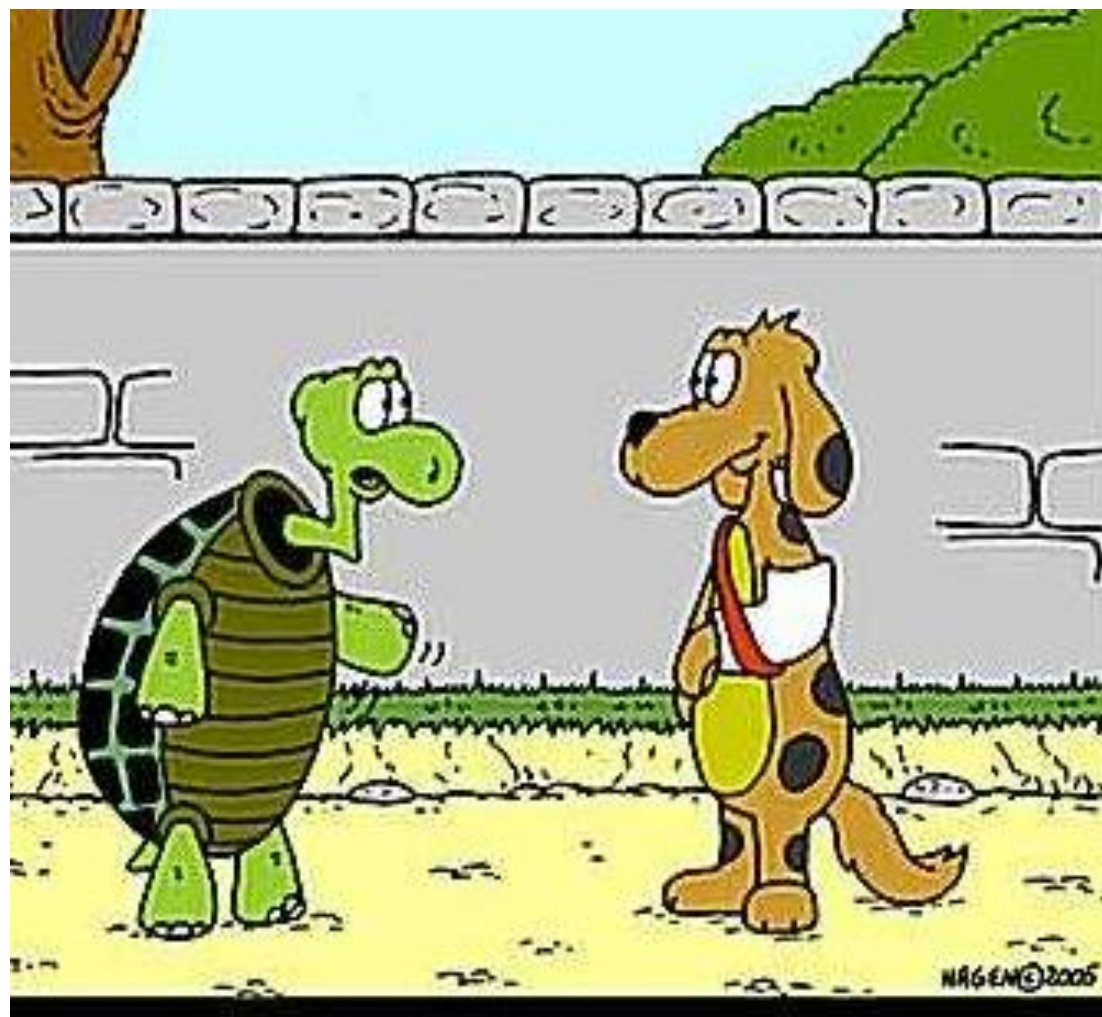
Amygdala: fear conditioning

Orbitofrontal Cortex: sensory integration, response inhibition

Anterior Cingulate: emotional responses

Posterior Insula: viscerosensory

No sensory cortex!



Don't talk to me about
having an itch you can't scratch...

Management of Itch Symptoms

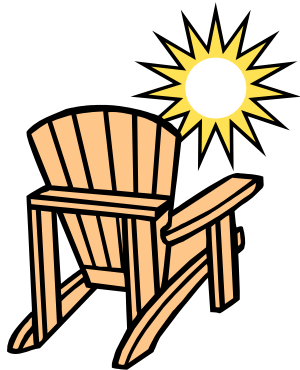
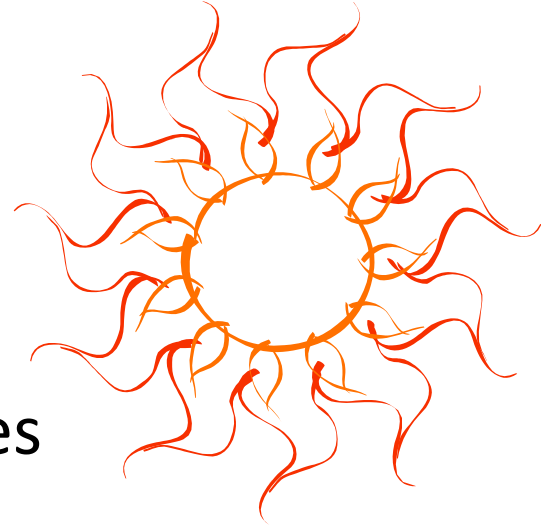


“I don't like taking medicine”

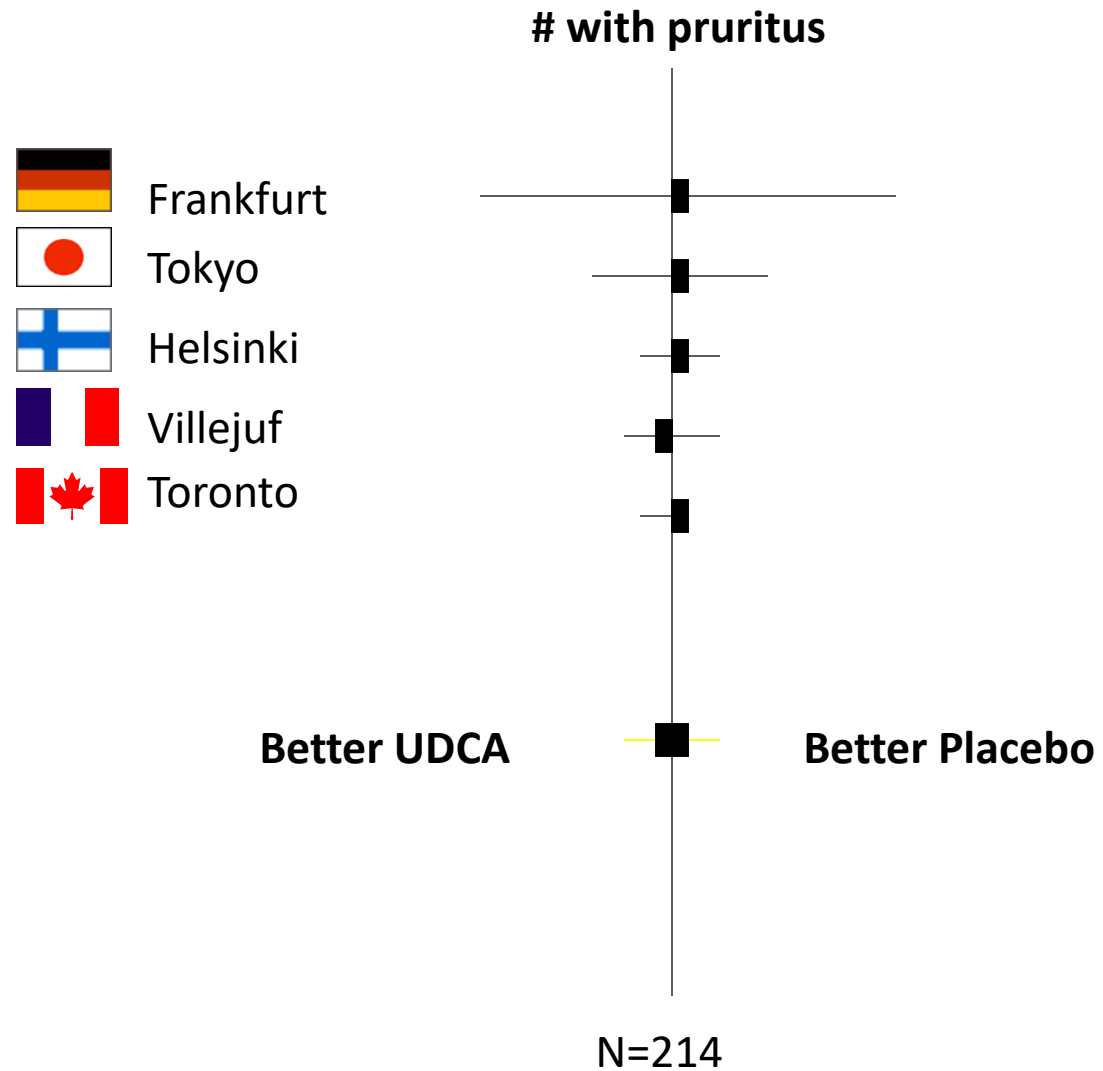
- **Loose, absorbent clothes**
- **Frequent use of emollients**
- **Avoid precipitants (narcotics)**
- **Trim nails**
- **Cool (not dry) environment/ showers/packs**
- **Controlled sun exposure**

Ultraviolet Rays

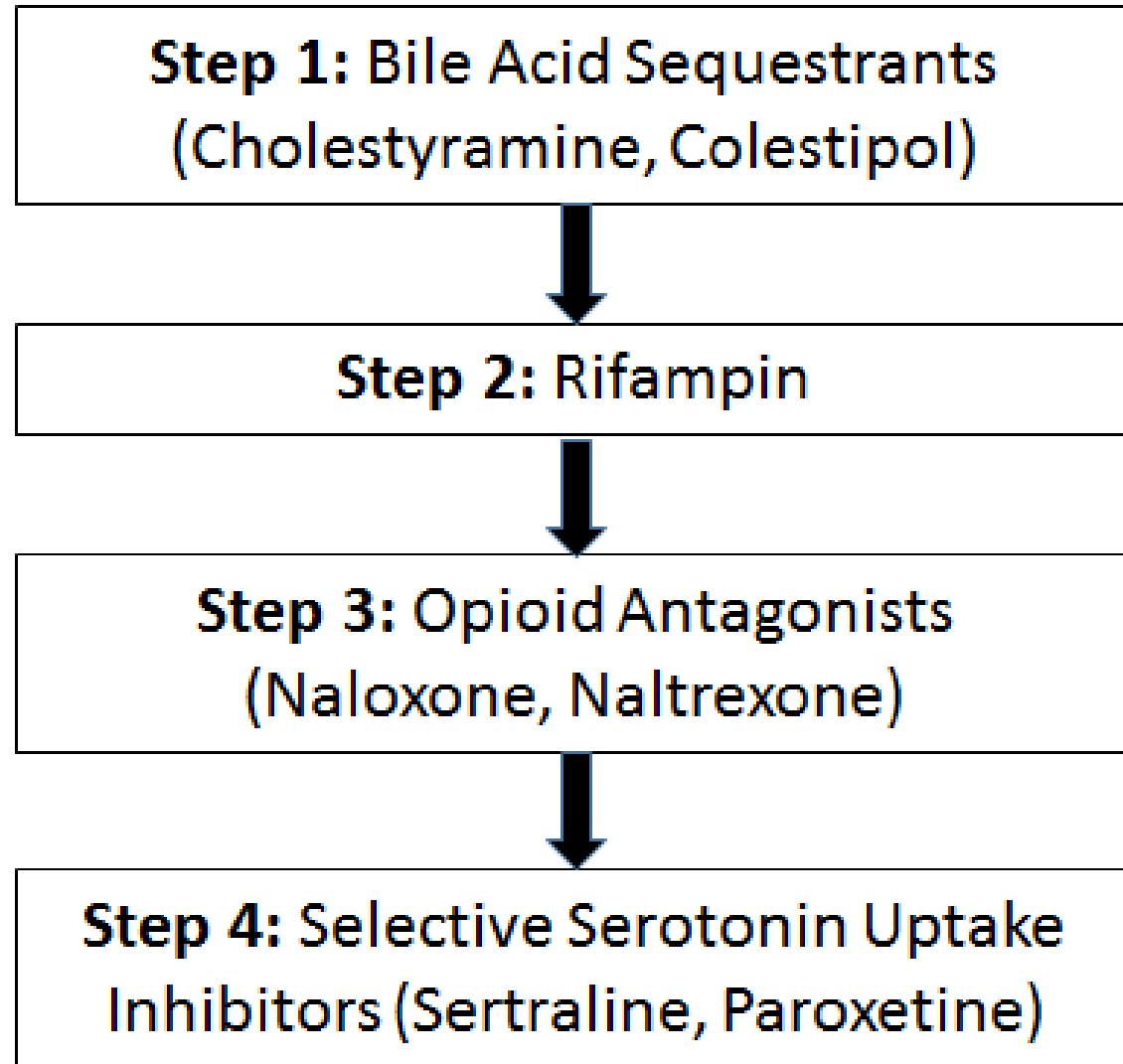
- Inhibits release of histamine and proliferation of mastocytes
- Mobilizes bile and uremic salts from skin
- Increases [BA] in urine
- Hanid, Lancet ,1980 N=6 PBC
 - onset 1 week, duration 2 weeks



Effect of Urso on Pruritus in PBC



“OK, It’s bad enough for me to take something now”

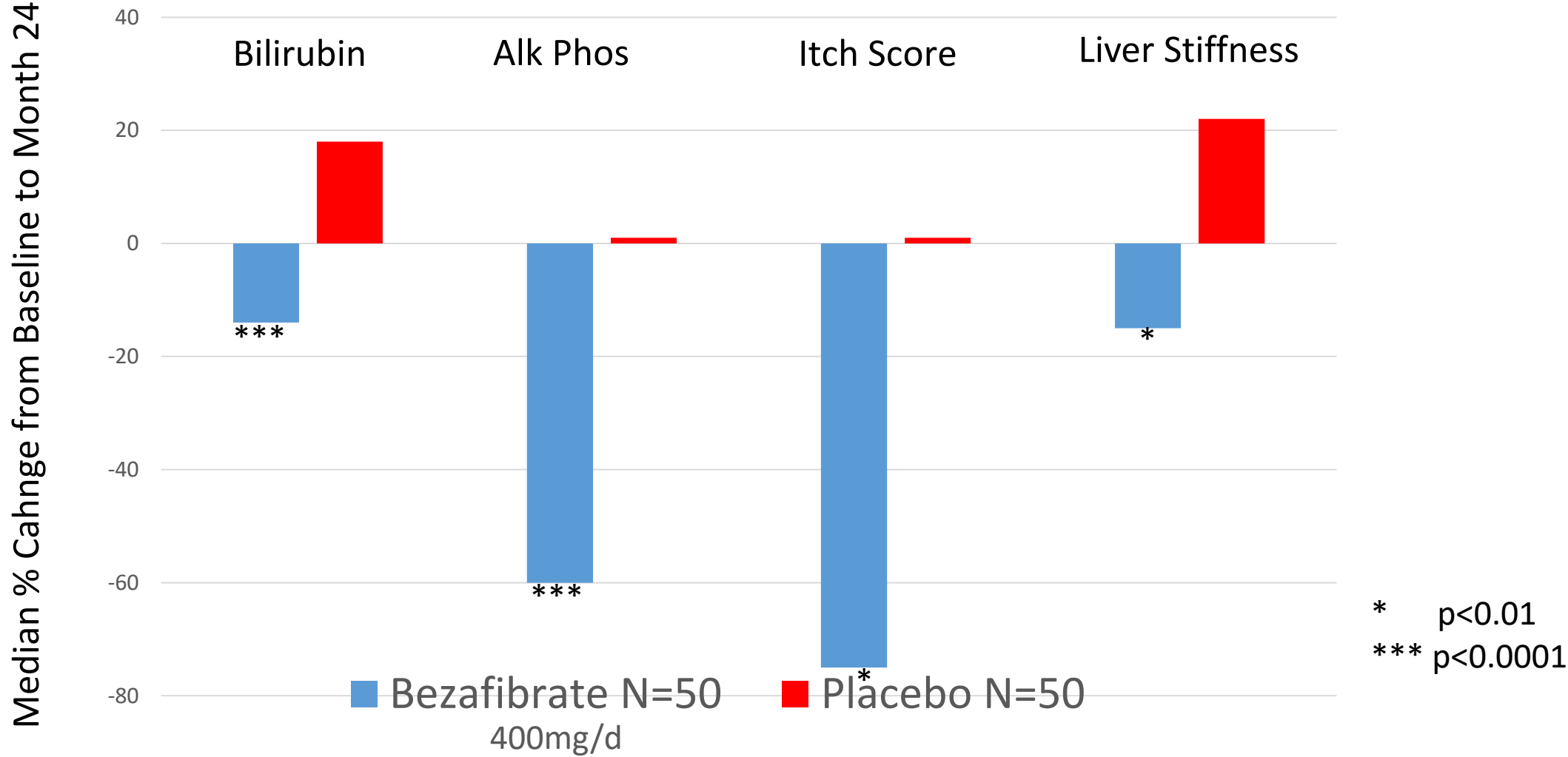


Medication	Dose	Notes
Cholestyramine	4 to 16 mg daily	Side effects include bloating, constipation, and unpleasant taste. May affect the absorption of other medications, and should be dose 1 hour prior or 3-4 hours after other medications.
Colestipol	2 to 16 mg daily	Similar to cholestyramine.
Rifampin	150 to 600 mg daily	Side effects include rash, fever, nausea, vomiting, and elevated liver enzymes. May affect the metabolism of other medications, such as warfarin, digitoxin, and tacrolimus.
Naltrexone	25 to 50 mg daily	Side effects include nausea, dizziness, flushing, drowsiness, and muscles cramps. Should not be used on patients taking chronic opiates.
Sertraline	75 to 100 mg daily	Side effects include irritability, insomnia, loose stool, and decreased libido.

What's New: Clinical Trials for Itching in PBC

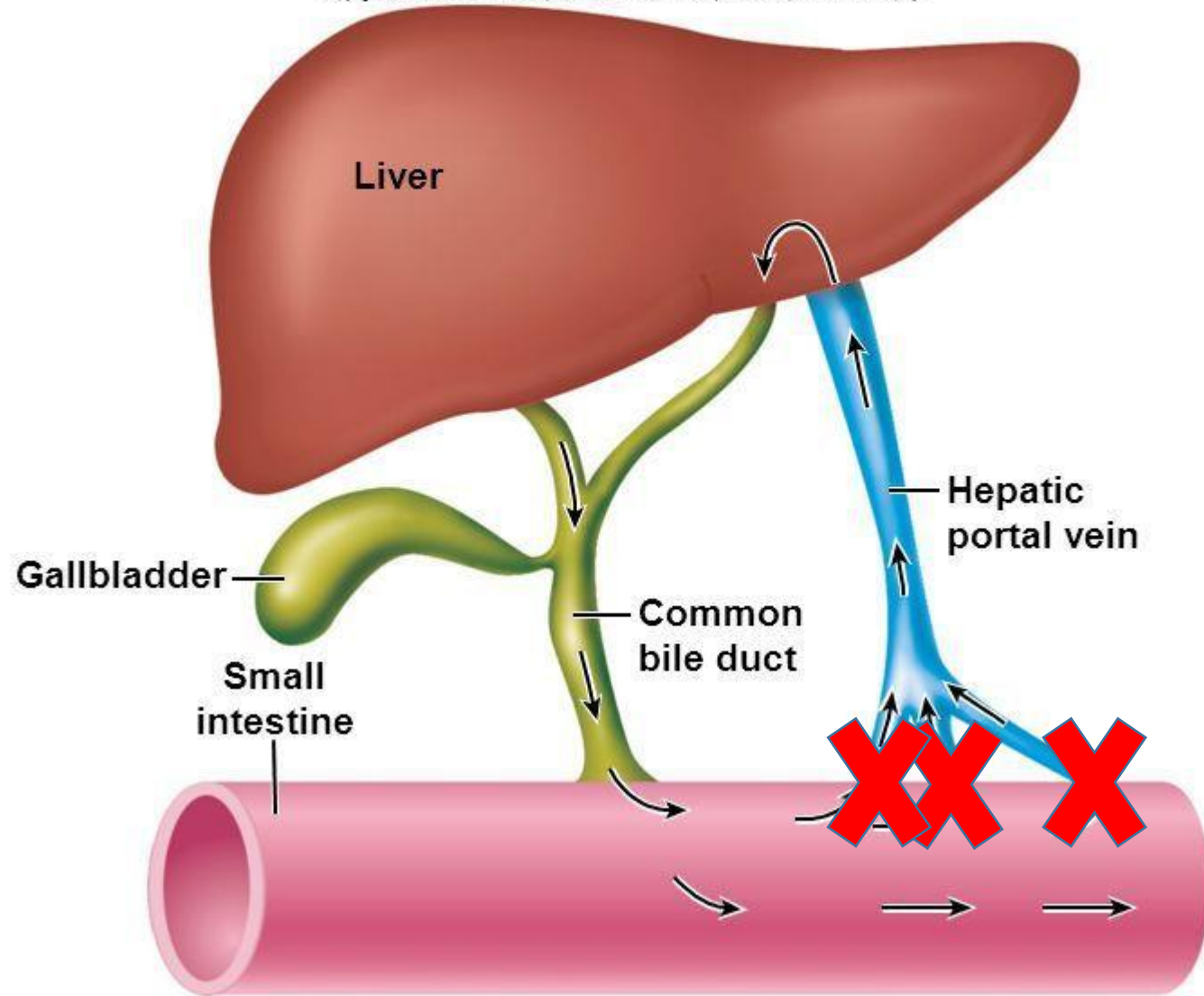
1. The Effect of Bezafibrate on Cholestatic Itch- Netherlands
2. GLIMMER-Dose Response Study of GSK2330672 for the Treatment of Pruritus in Patients With Primary Biliary Cholangitis
66 sites in US and Europe. (Texas sites are San Antonio, Dallas)

Bezafibrate Improves Cholestasis, Symptoms, and Fibrosis in PBC Suboptimal Ursodiol Responders



Enterohepatic Circulation

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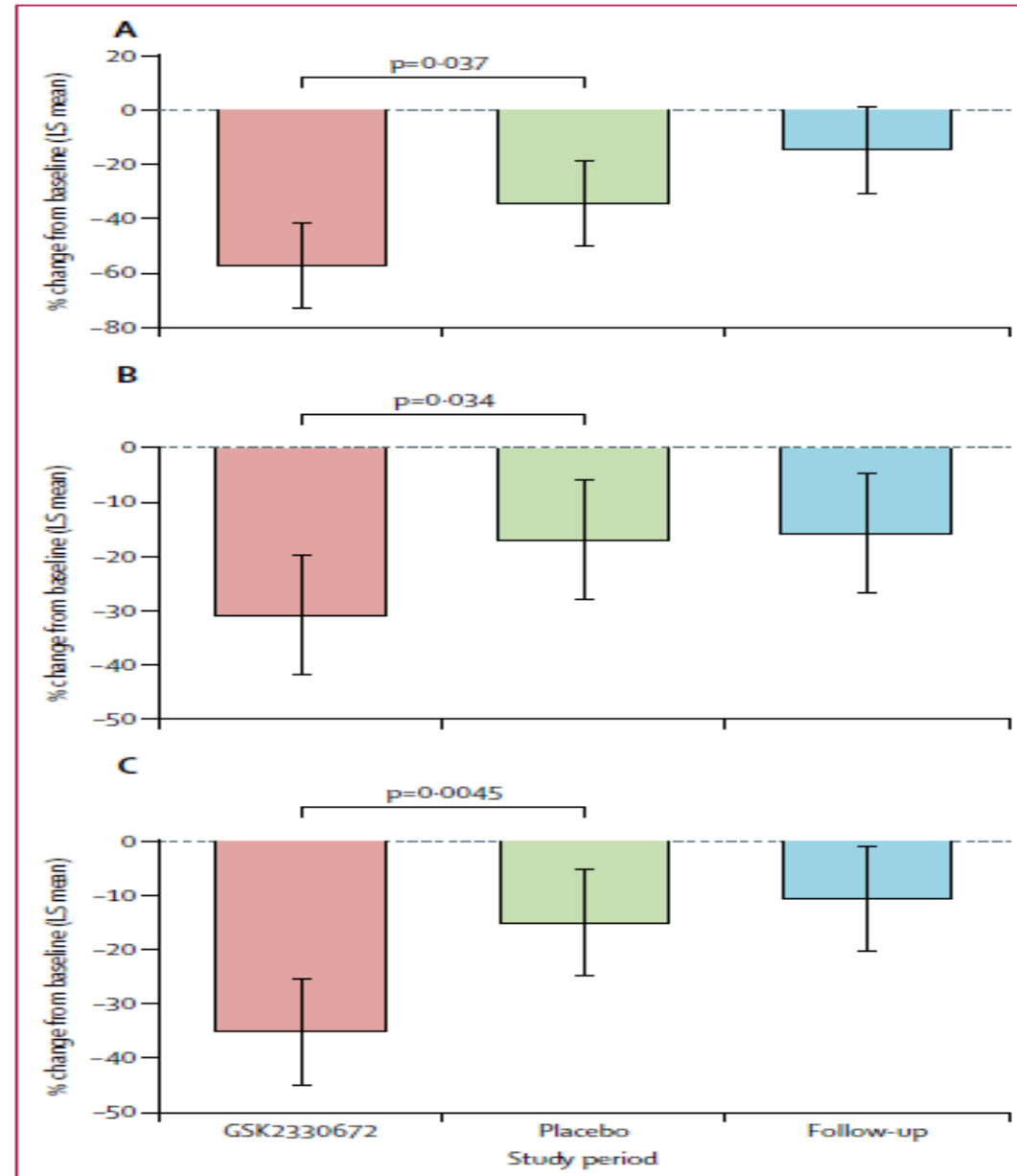


Improvement in Itch with Bile Acid Uptake Inhibitor

1-10 scale

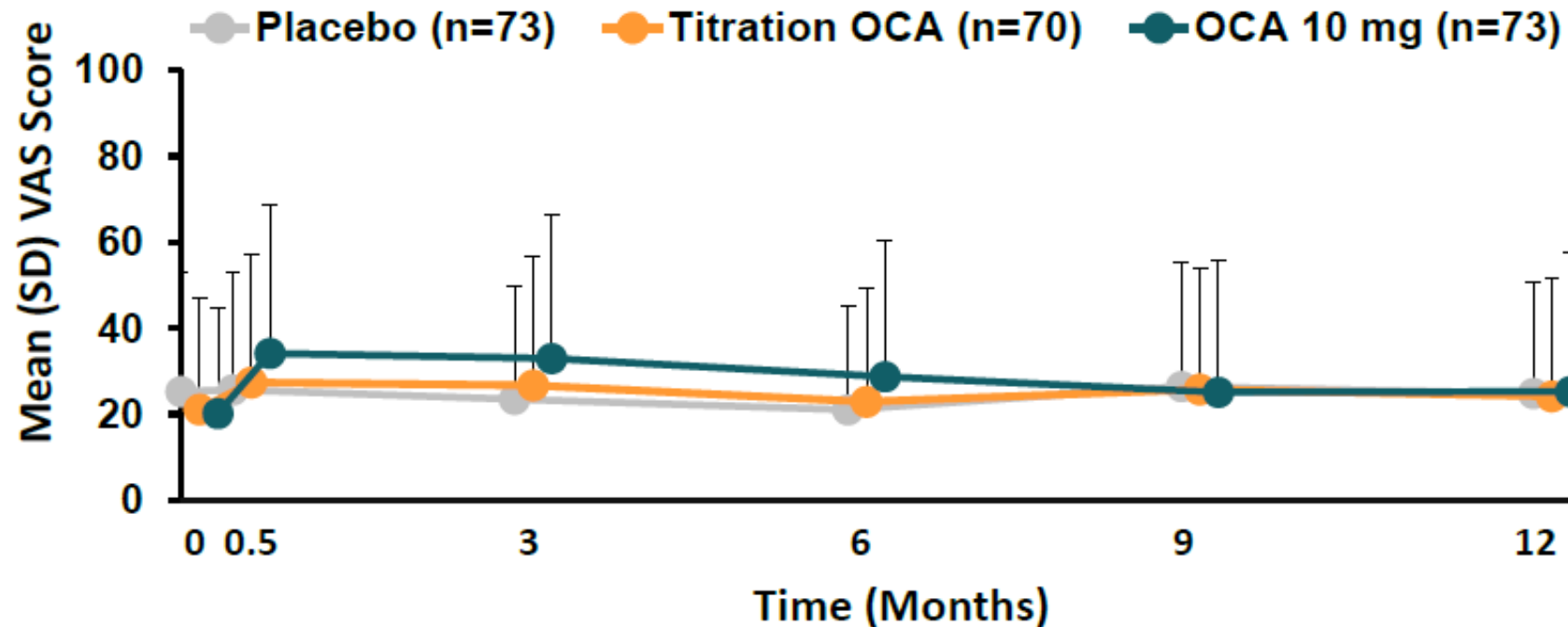
PBC-40 Itch

5-D Itch

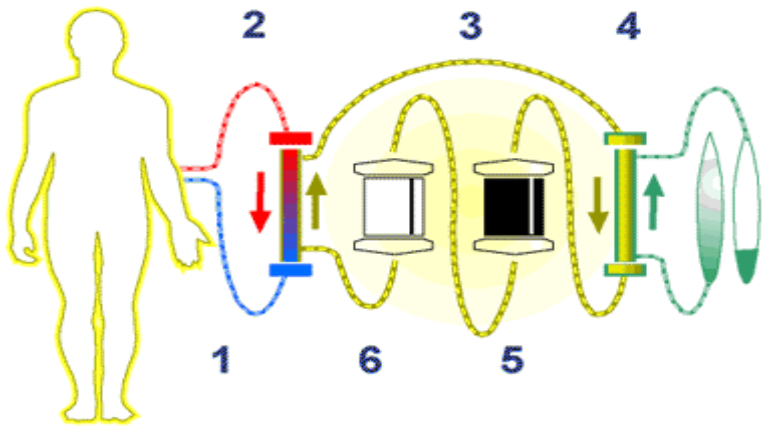


Itching with Obeticholic Acid (OCA)

	Placebo (n=73)	Titration OCA (n=70)	OCA 10 mg (n=73)
Patients reporting at least 1 treatment-emergent adverse event (TEAE) Pruritus Event, n (%)	28 (38)	39 (56)	51 (70)
Discontinuations due to Pruritus, n(%)	0	1 (1)	7 (10)
Pruritus Events by Maximum Severity, n (%)			
Mild	16 (22)	11 (16)	15 (21)
Moderate	7 (10)	15 (21)	19 (26)
Severe	5 (7)	13 (19)	17 (23)



When Medications Fail...



MARS (Molecular Adsorbents Recirculating System)/
Plasmapheresis



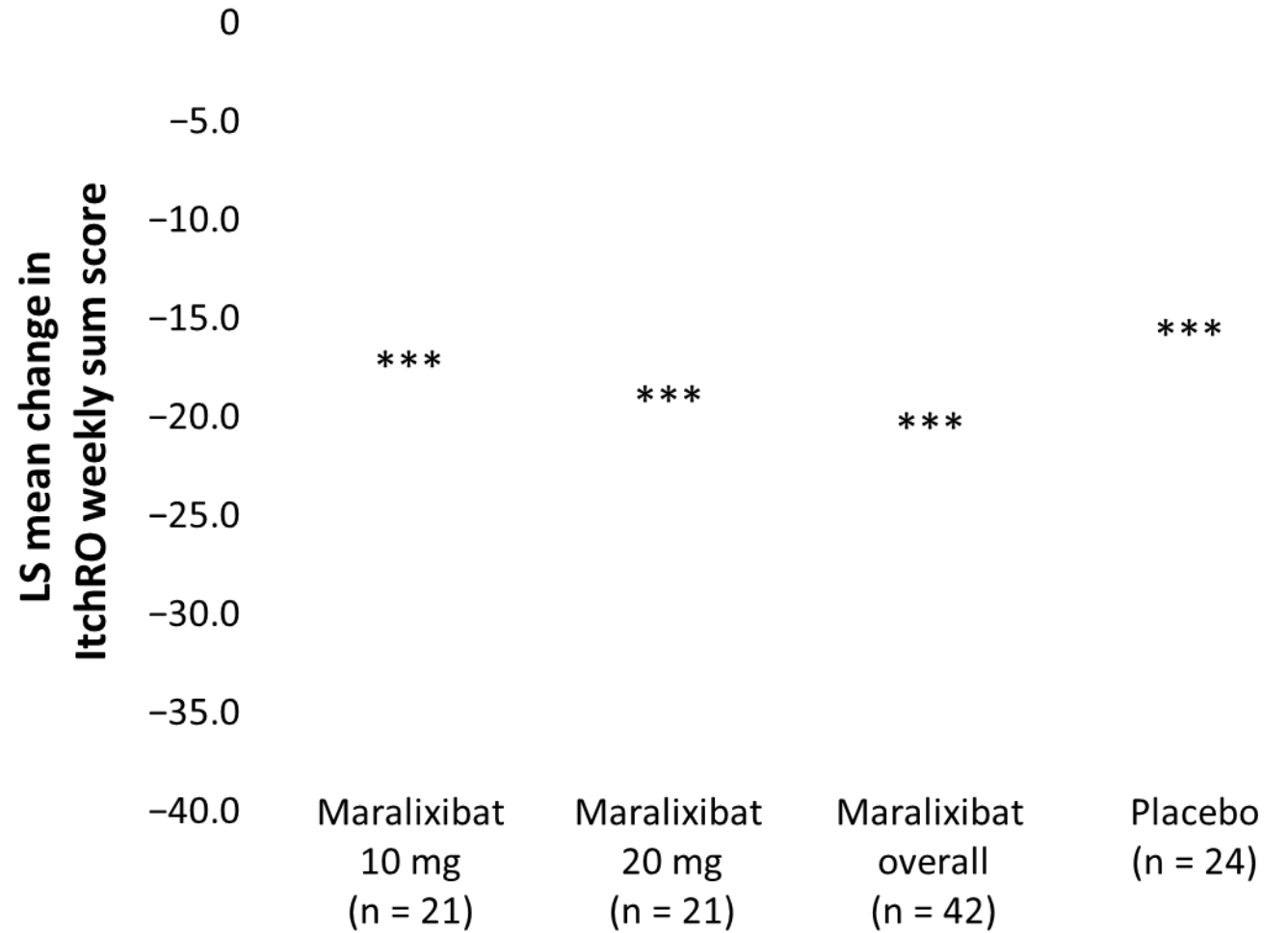
Nasobiliary Drainage



Liver Transplantation

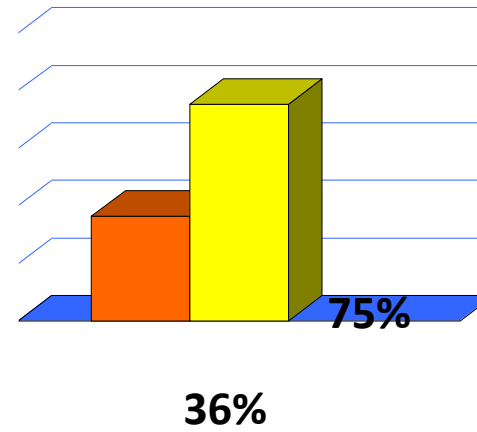
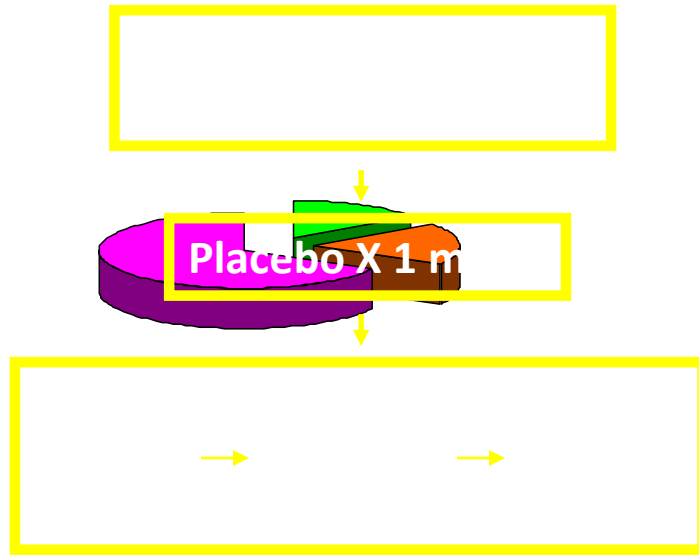


- Maralixibat 10 mg: -25.63 *
- Maralixibat 20 mg: -27.34*
- Placebo: - 23.36*



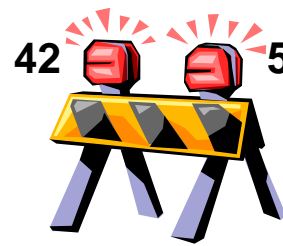
Bile Acid Binding Resins

- Extensive clinical experience since 1966
- Excellent safety profile
- Poor tolerability



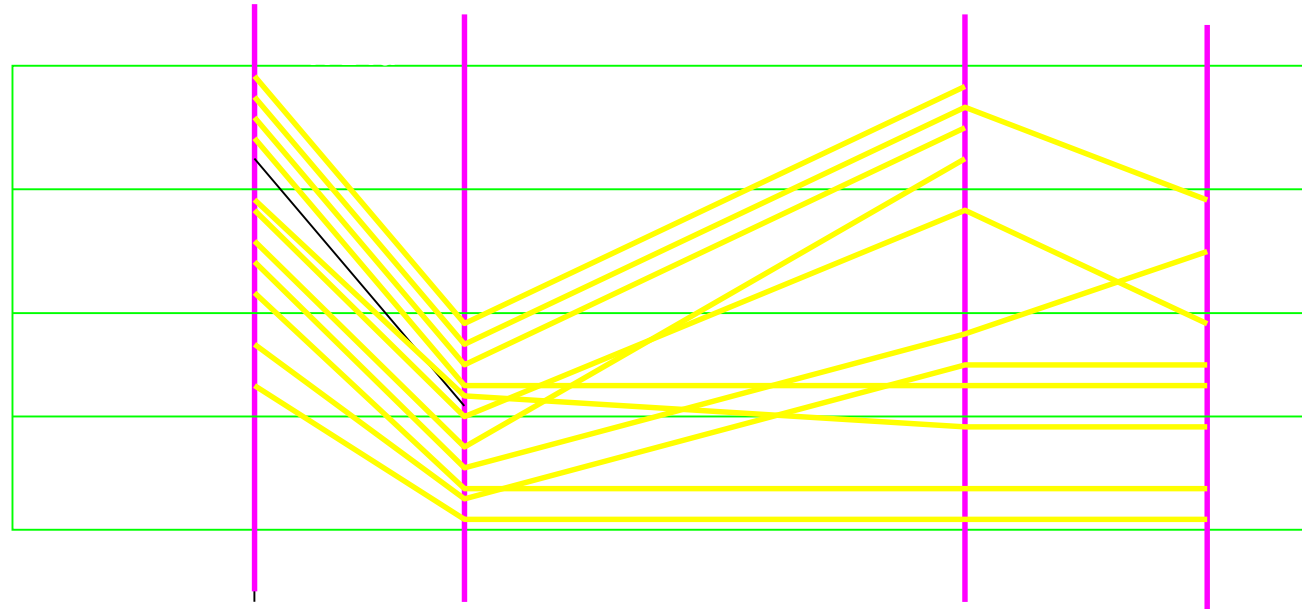
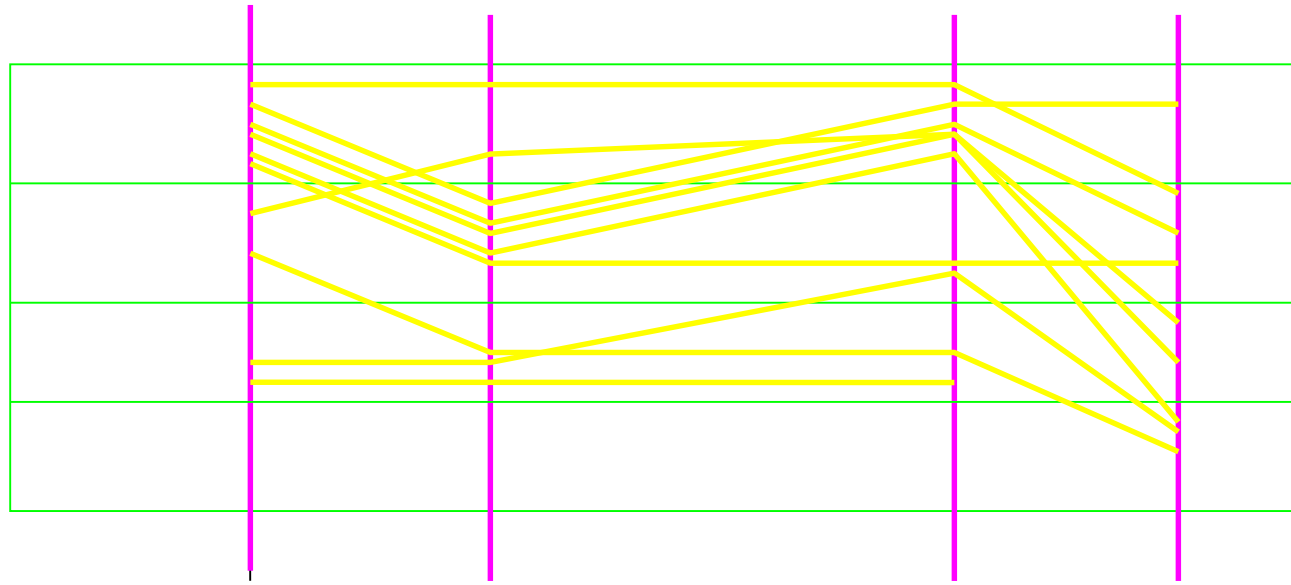
Rifampicin

Source	Dose	N=	Prefer Rifampin	Prefer Placebo	No Preference	P value
Ghent, 1988	300-450 mg/d	9	8	1	0	0.04
Woolf, 1990	300mg/d	10	2	2	8	NS
Cynamon, 1990	10 mg/kg	5	5	0	0	0.06
Podesta, 1991	600 mg/d	14	12	0	2	<0.001
Bachs, 1989	10 mg/kg	17	15	2	0	0.002
Total		55	42	5	10	



Rare severe hepatotoxicity

Rifampicin is more Effective than Phenobarbitol

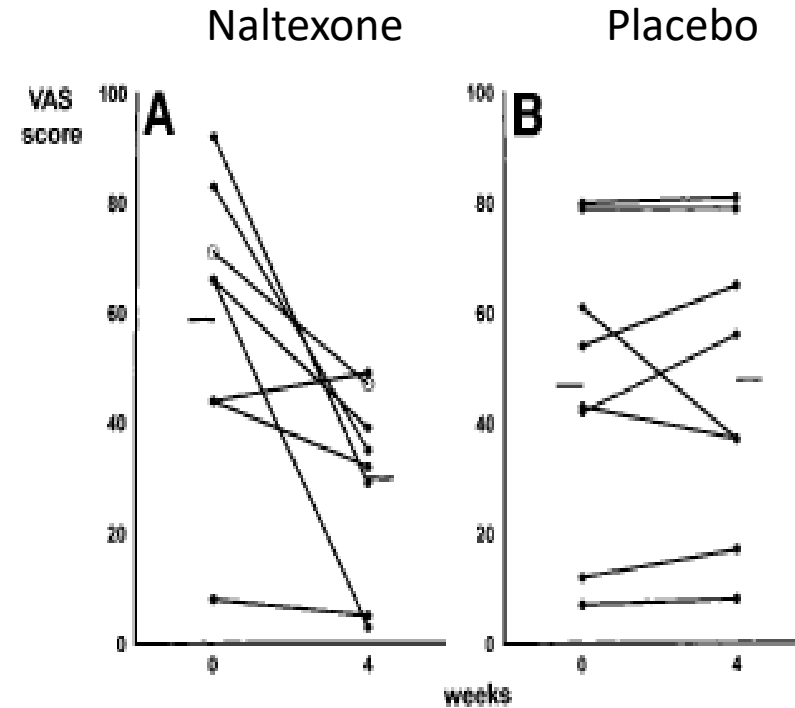


Opioid Receptor Blockers

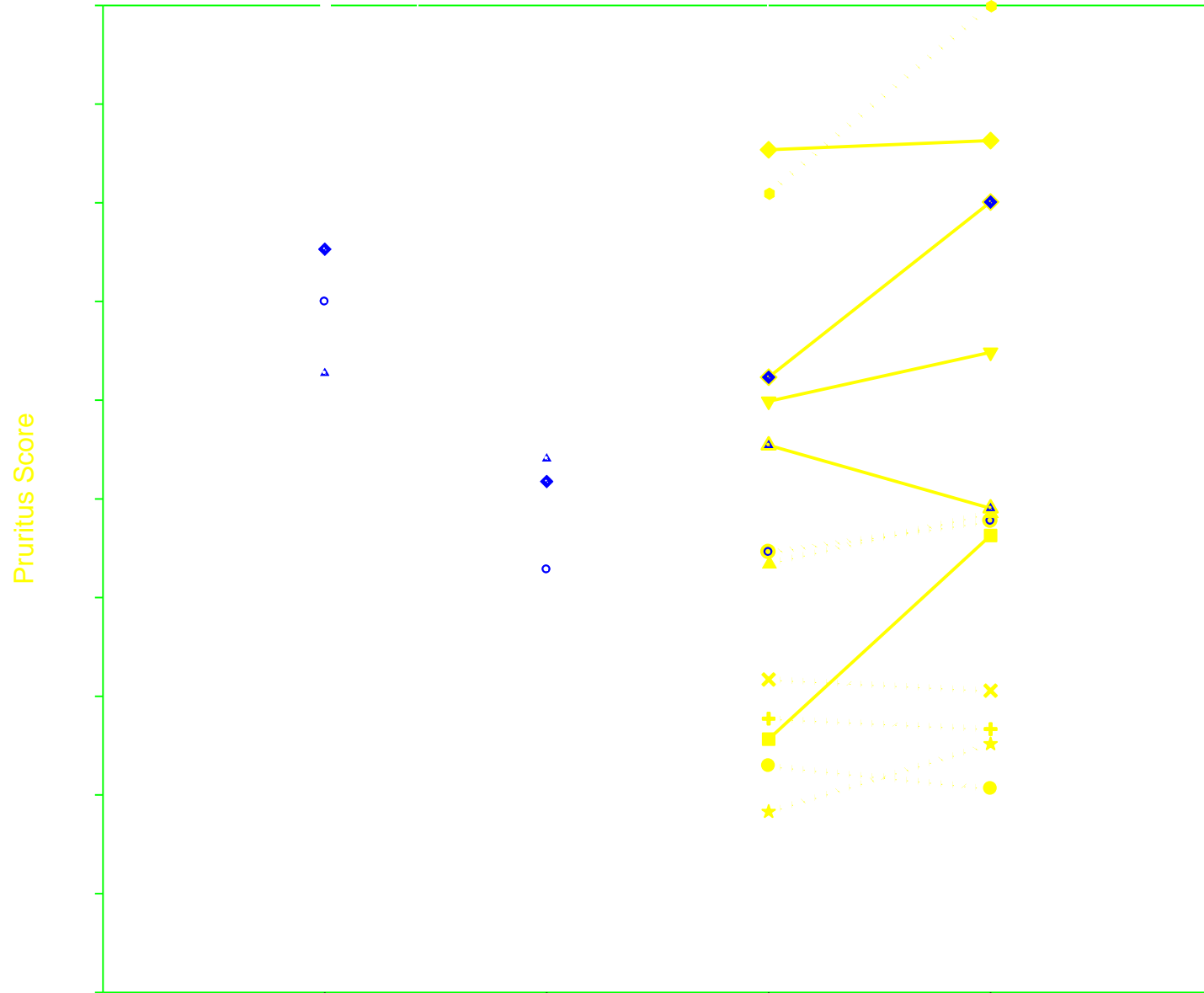
- Naltrexone 50 mg/d (12.5 mg 150 mg BID)
- 38%-93% response



- Side effects:
 - early: dizziness, headache, fatigue, nausea, abdominal pain, hypertension, clammy
 - late: chronic pain
- > 50% withdrawal
- 6%-36% breakthrough

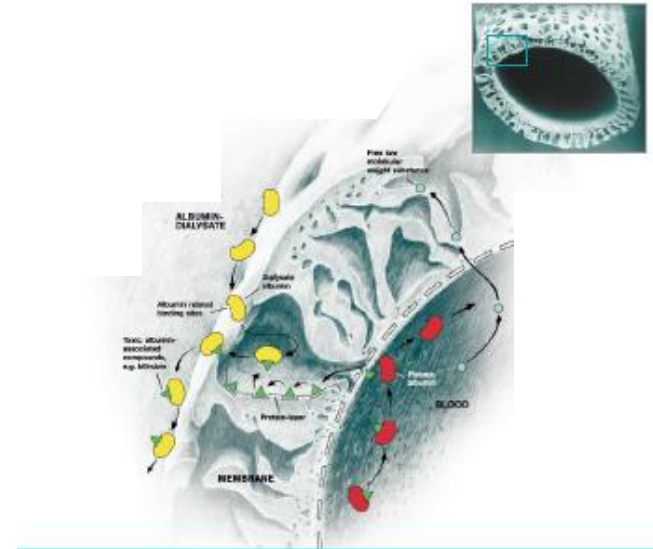
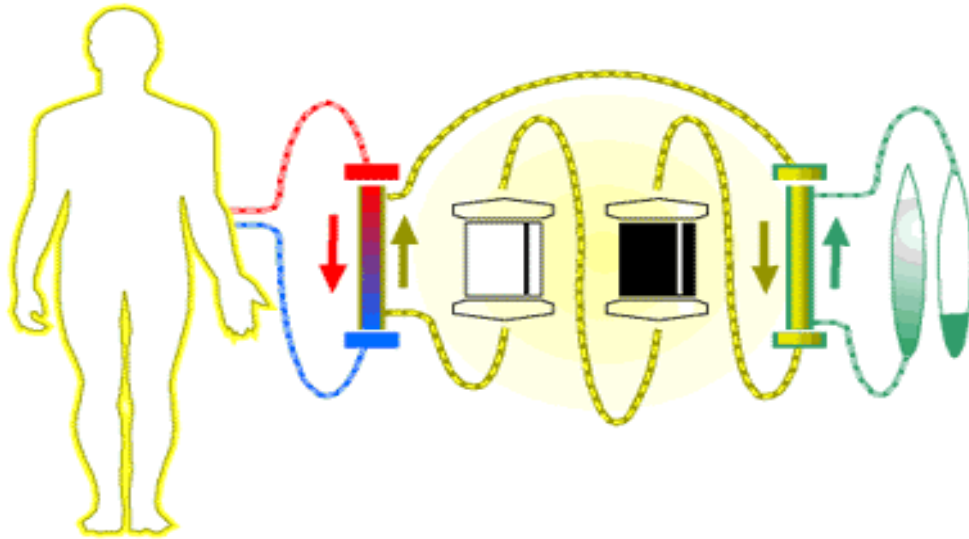


Placebo



MARS

Molecular Adsorbents Recirculating System



N=26 case reports

No controlled trials

In BRIC, PBC, HCV, DILI, biliary strictures, rejection

6-16 hrs/day X 1-10 days

Partial or complete relief in 25/26

Lasts few days to 18 months.