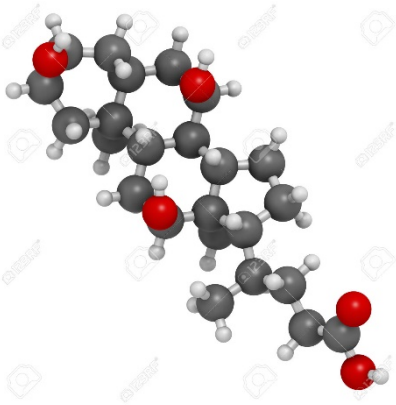


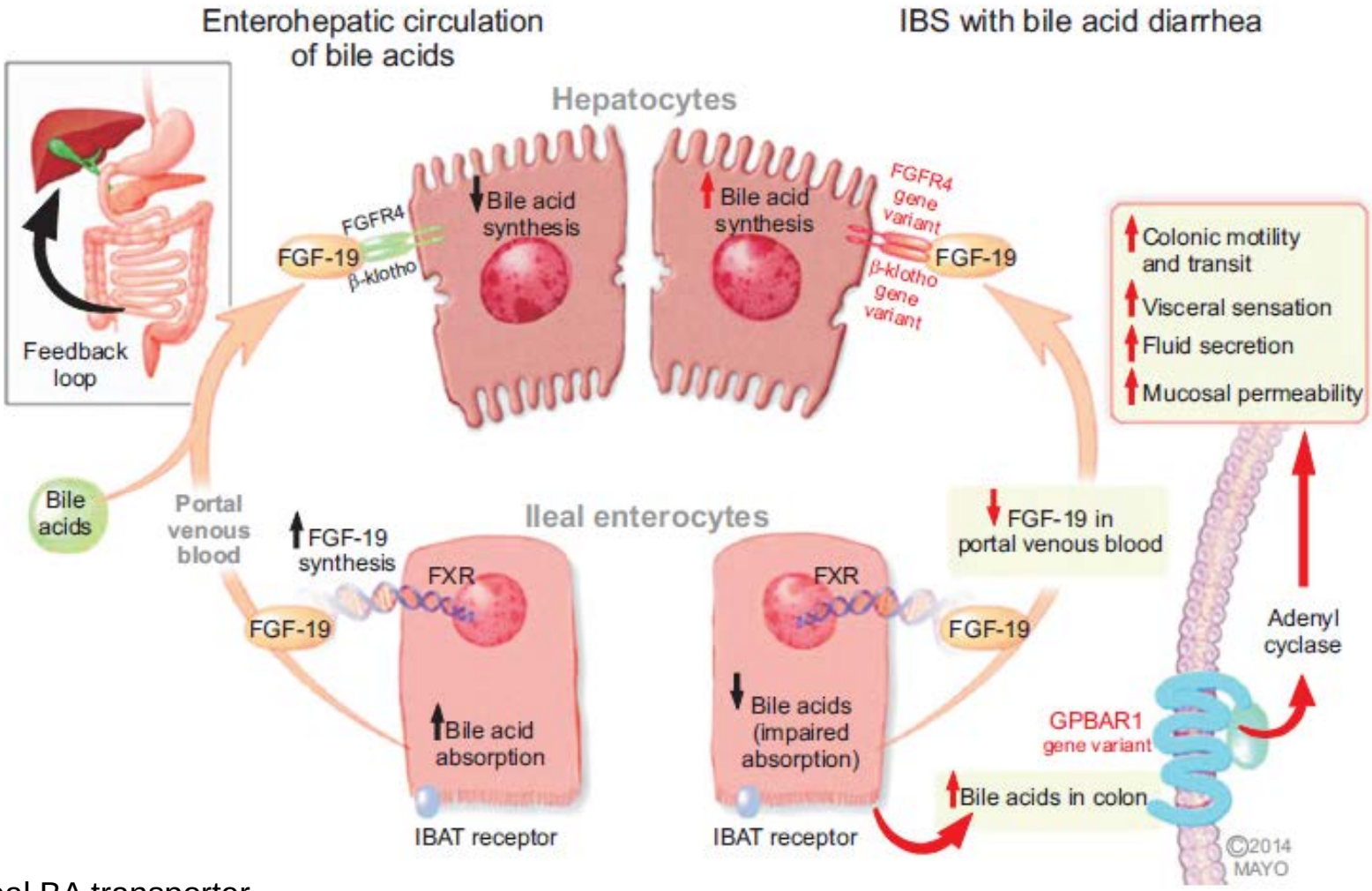
Ácidos biliares y síndrome del intestino irritable

Fermín Mearin

Centro Médico Teknon

Barcelona

Mechanisms of BA-related bowel dysfunction in IBS-D



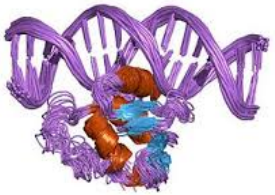
IBAT: ileal BA transporter
FGF-19: fibroblast growth factor 19
GPBAR1: G protein-coupled BA receptor 1

Camilleri. Gut & Liver 2015

Bile acid malabsorption in IBS-D

Bile acid malabsorption assessed by the 75SeHCAT test

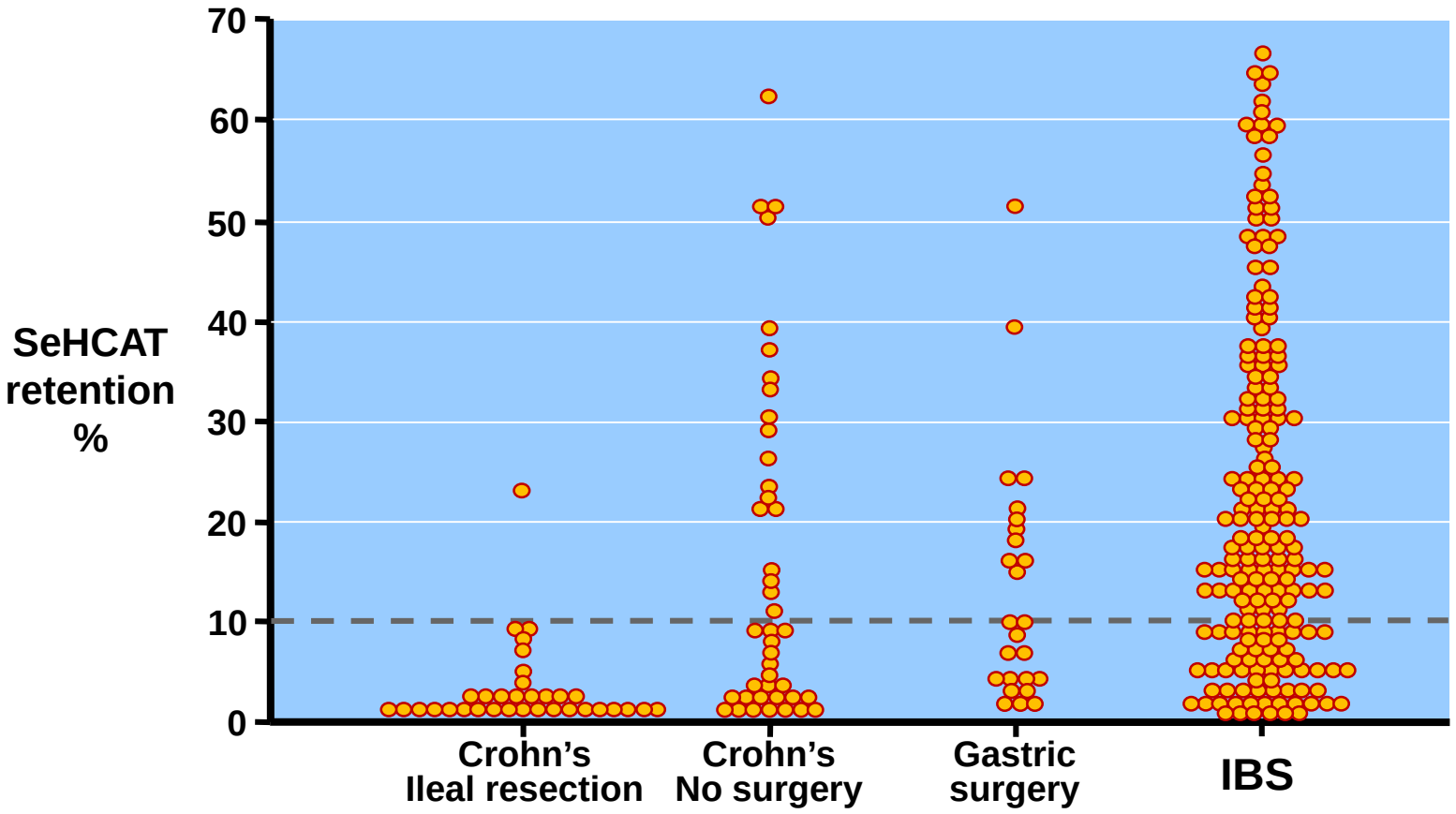
- **23 healthy adults**
- **38 IBS-D patients**



- **BA malabsortion in 50% of IBS-D patients**
- **40% colestyramine relieved diarrhea**

Sciarretta et al. Gut 1987

BA malabsorption in chronic diarrhoea



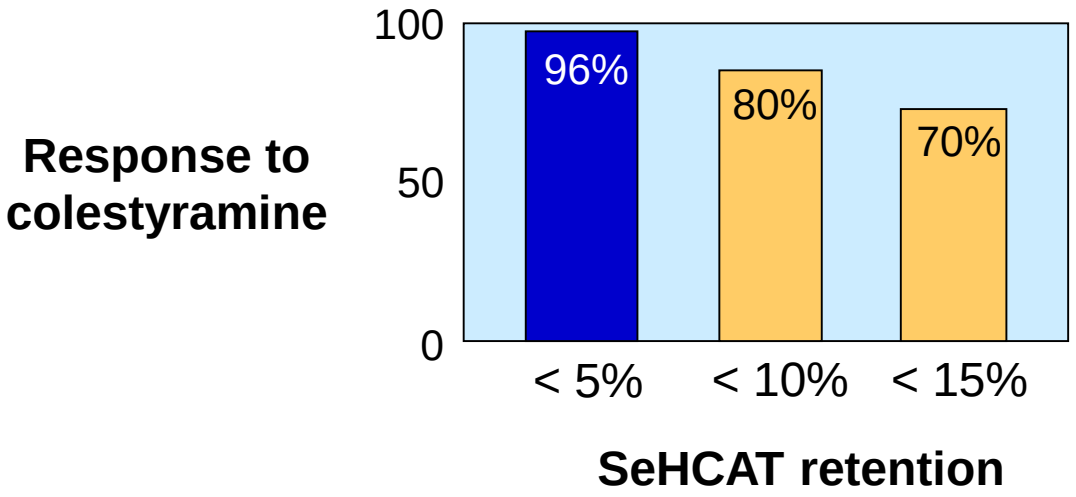
Smith et al. J R Coll Physicians Lond 2000

Prevalence of idiopathic BA malabsorption in IBS-D

(Systematic review)

18 relevant studies, 15 prospective, 1223 patients

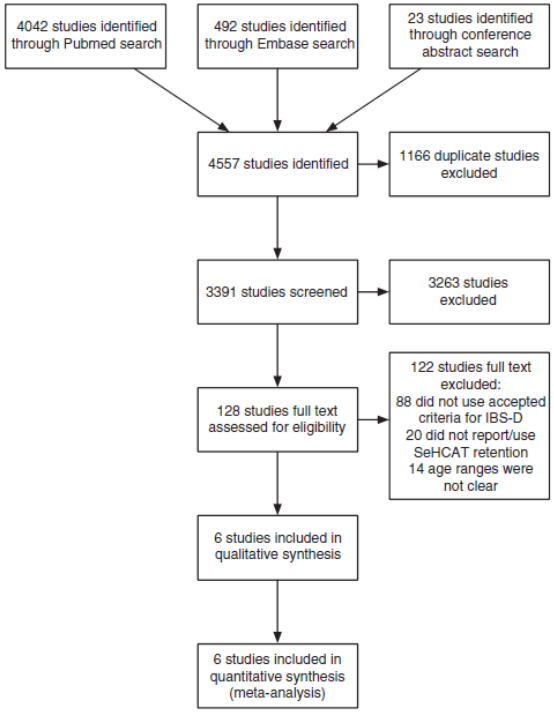
- 10% (CI: 7-13) patients had severe BAM
- 32% (CI: 29-35) patients had moderate BAM
- 26% (CI: 23-30) patients had mild BAM



Wedlake et al. APT 2009

AP&T Alimentary Pharmacology and Therapeutics

Systematic review with meta-analysis: prevalence of BA malabsorption in IBS-D



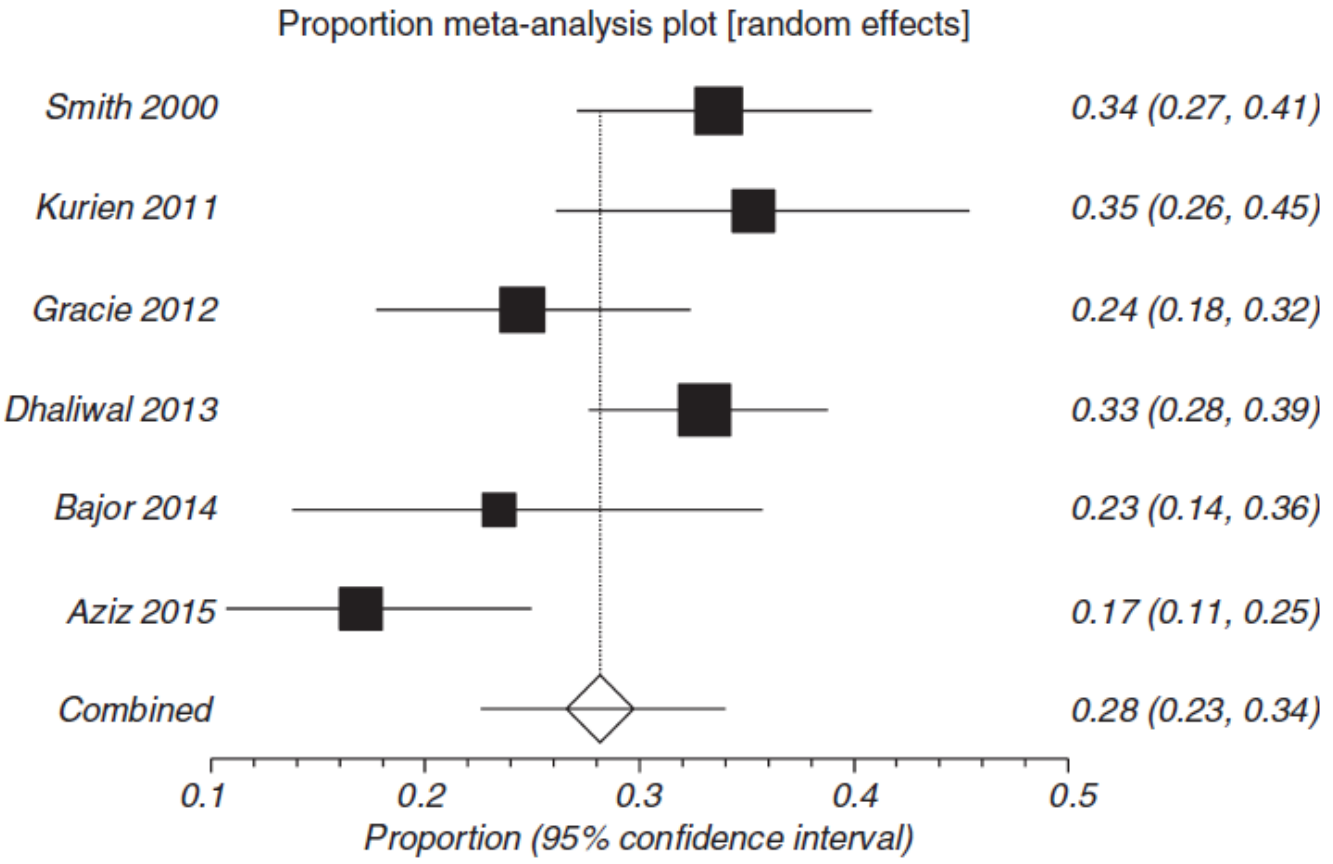
Quality Assessment for Diagnostic Accuracy Studies

	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow & timing	Patient selection	Index test	Reference standard
Smith *et al.*[23]	+	+	+	+	+	+	+
Kurien *et al.*[24]	?	+	−	+	?	+	?
Gracie *et al.*[21]	?	+	−	+	+	+	?
Dhaliwal *et al.*[22]	?	+	+	+	+	+	+
Bajor *et al.*[25]	+	+	+	+	?	+	+
Aziz *et al.*[26]	+	+	+	+	?	+	+

Slattery et al. APT 2015

Bile acid malabsorption in IBS-D

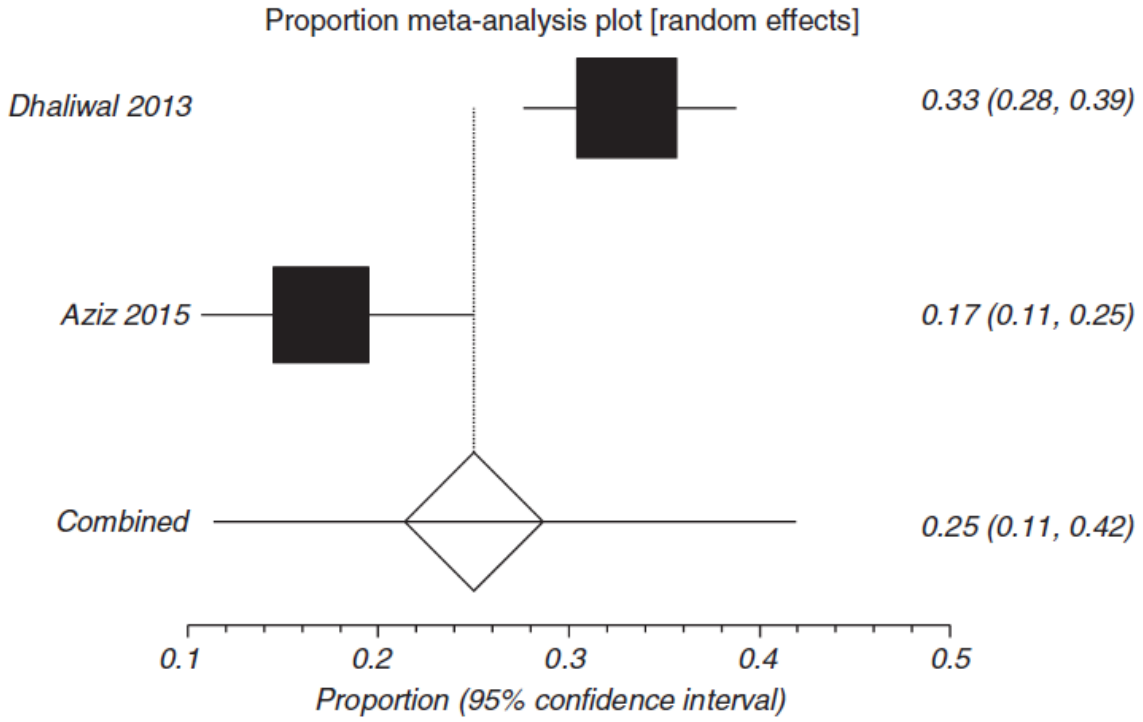
Proportions of BAM in 908 patients with IBS-D



Slattery et al. APT 2015

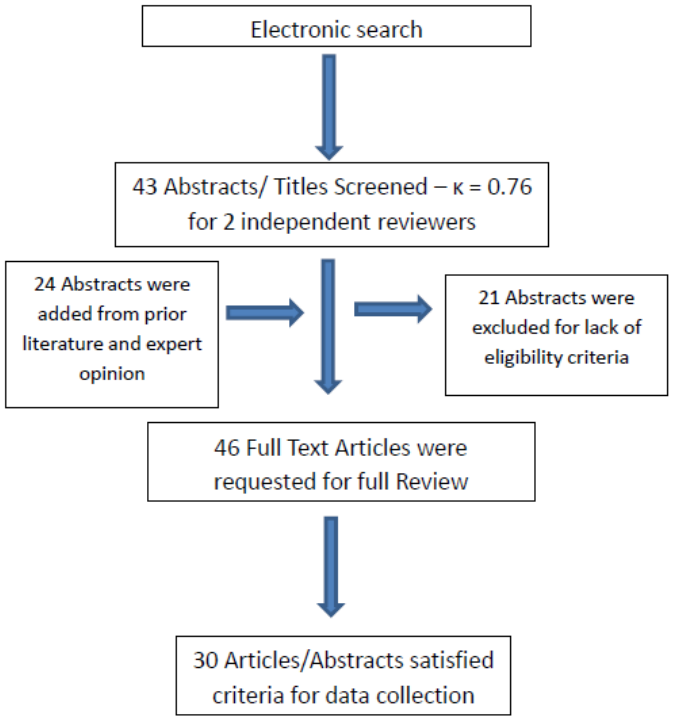
Bile acid malabsorption in IBS-D

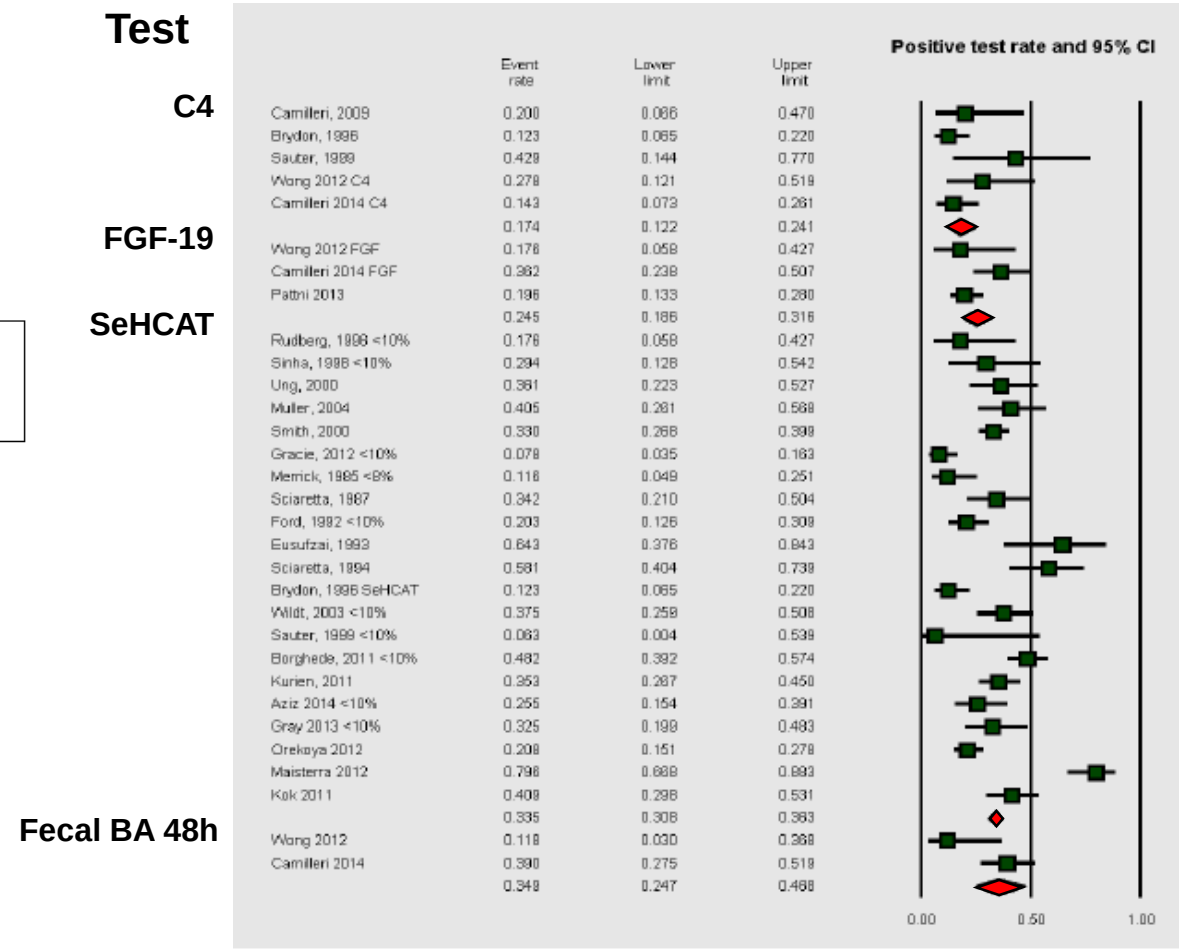
BAM in prospective studies using the Rome III criteria for IBS-D



Slattery et al. APT 2015

Biomarkers for BA-diarrhea in IBS-D and FDr
Systematic review and meta-analysis





C4: 7α-hydroxy-4-cholesten-3-one
FGF-19: fibroblast growth factor 19

Valentin et al. AJG 2016

Increased fecal primary BA and dysbiosis in IBS-D

- 14 IBS-D
- 18 Healthy volunteers

- % of fecal primary BA was significantly higher in IBS-D vs HS
- It was significantly correlated with stool consistency and frequency

- ↑ Escherichia coli and ↓Leptum and Bifidobacterium in IBS-D

As the gut microbiota is the exclusive pathway to transform primary into secondary BA, this suggests a functional consequence of dysbiosis, leading to lower BA transformation.

Duboc et al. Neurogastroenterol Motil 2011

Increased BA synthesis is associated with IBS-D

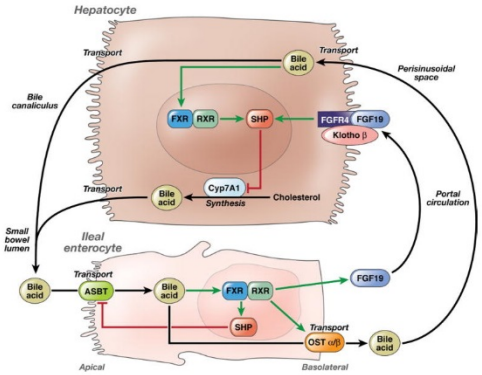
- **26 healthy volunteers**
- **26 patients with IBS-C**
- **26 patients with IBS-D**

Serum levels of 7α-hydroxy-4-cholesten-3-one (C4; a surrogate for BA synthesis)
Fibroblast growth factor (FGF) 19 (an ileal hormone that downregulates BA synthesis)
Concentration of BA in stools

IBS-D: ↑ [BA] in stool & serum C4 levels

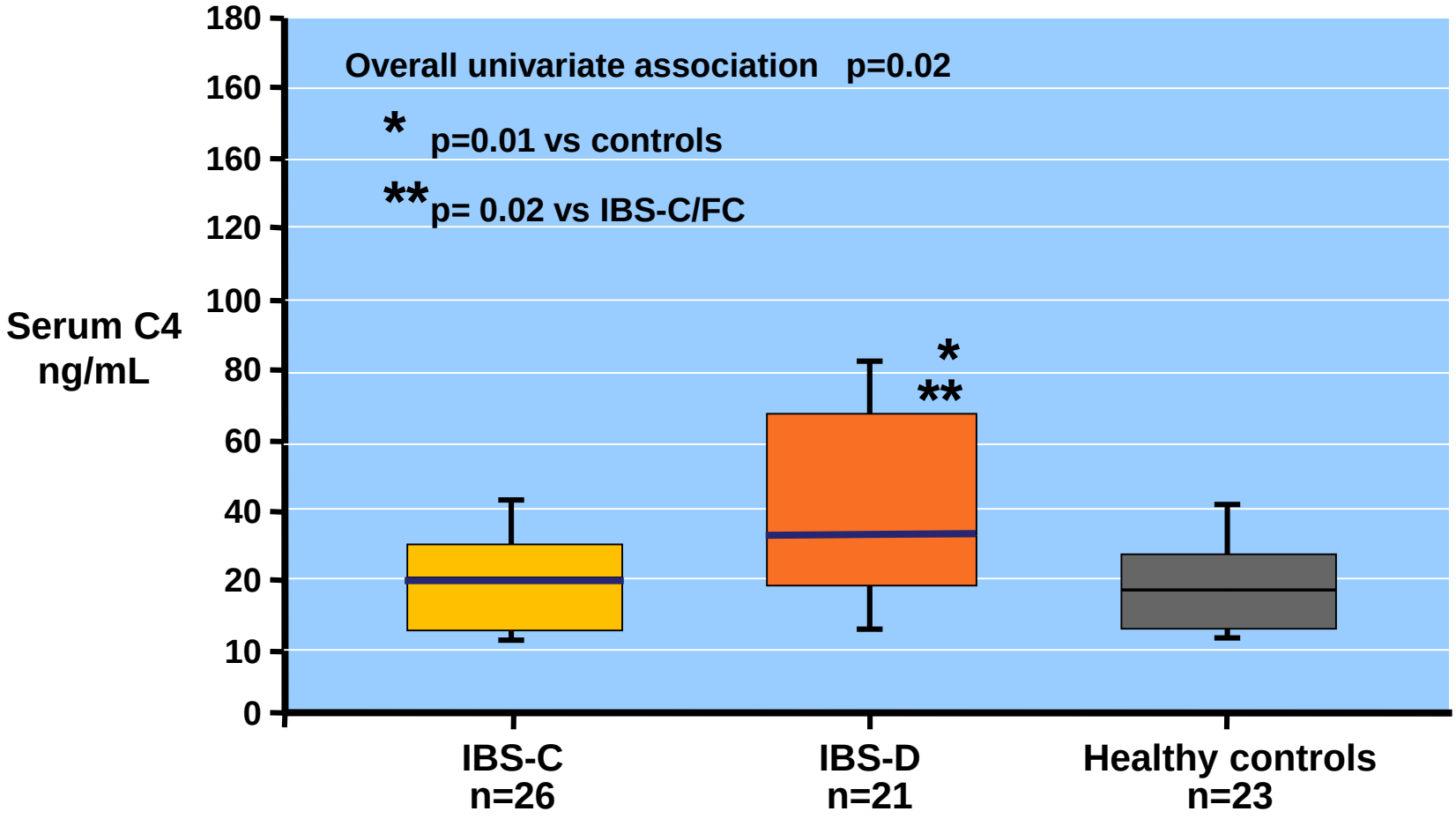
38% of patients with IBS-D had increased serum levels of C4

FGFR4 rs1966265 was associated with stool level of BA (*P* = .032).



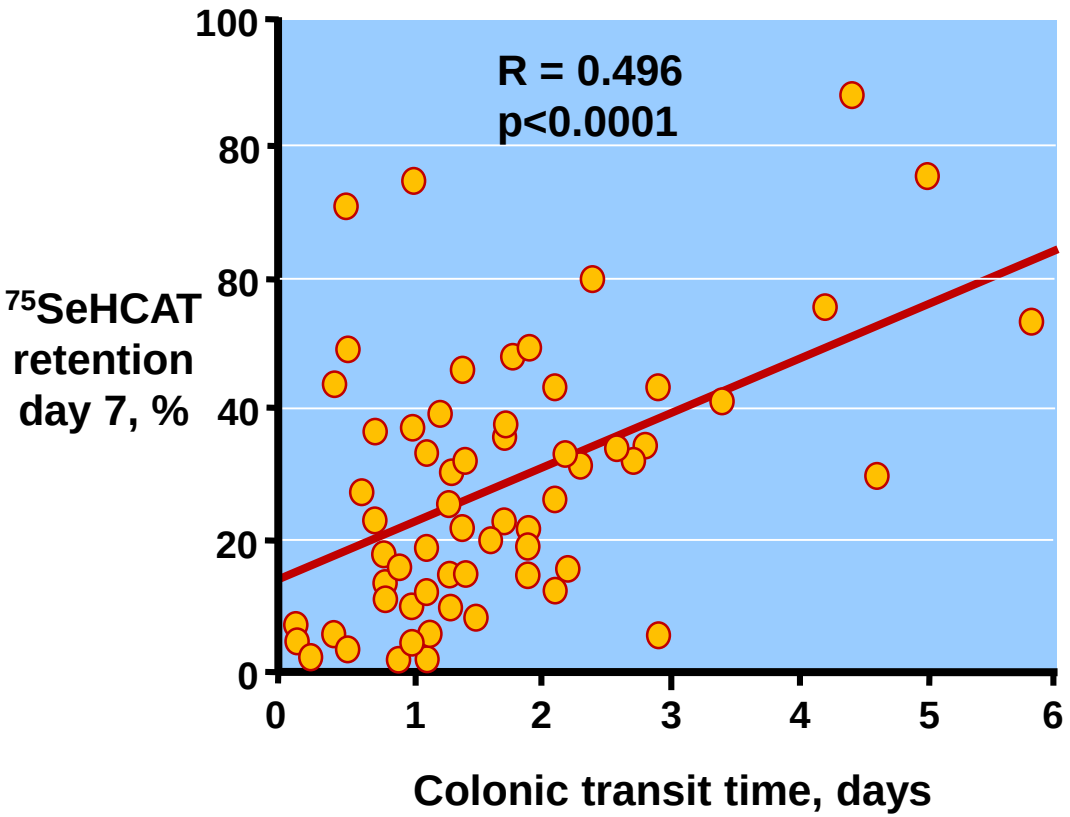
Wong et al. Clin G & H 2012

Increased BA synthesis in IBS-D



Wong et al. Clin G & H 2012

Colonic bile acids are related to colonic transit in IBS



Abnormal SeHCAT retention

- ↑ Stool frequency
- Looser stools
- Accelerated (left) colonic transit
- ↑ C4
- ↓ FGF19
- ↑ Body Mass Index
- ↑ Triglycerides
- ↓ HDL Cholesterol
- Rectal hyposensitivity

Bajor et al. Gut 2014

Colonic transit and BA synthesis/excretion in IBS-D without BA malabsorption

116 patients with IBS-D

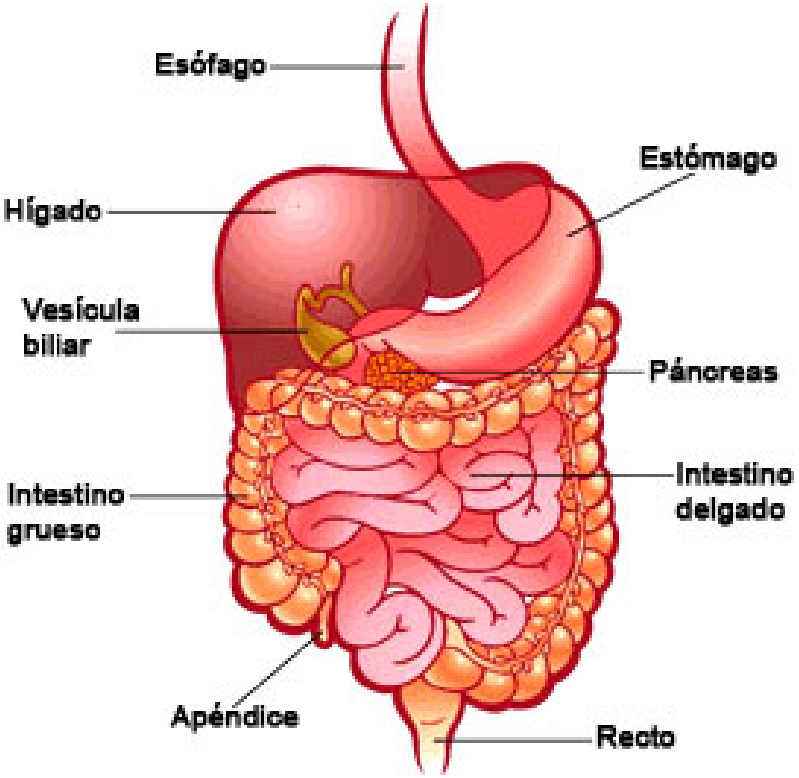
- ✓ **Total and individual main fecal BA excretion**
- ✓ **Fecal fat**
- ✓ **Fecal weight over 48 hours**
- ✓ **Fasting serum levels of C4**
- ✓ **Colonic transit by scintigraphy**

IBS-D without overt BAM (normal 48-hour total fecal BA or serum C4)

Positive correlations between total fecal BA, fecal primary and secretory BA, and colonic transit time ($P < .0036$)

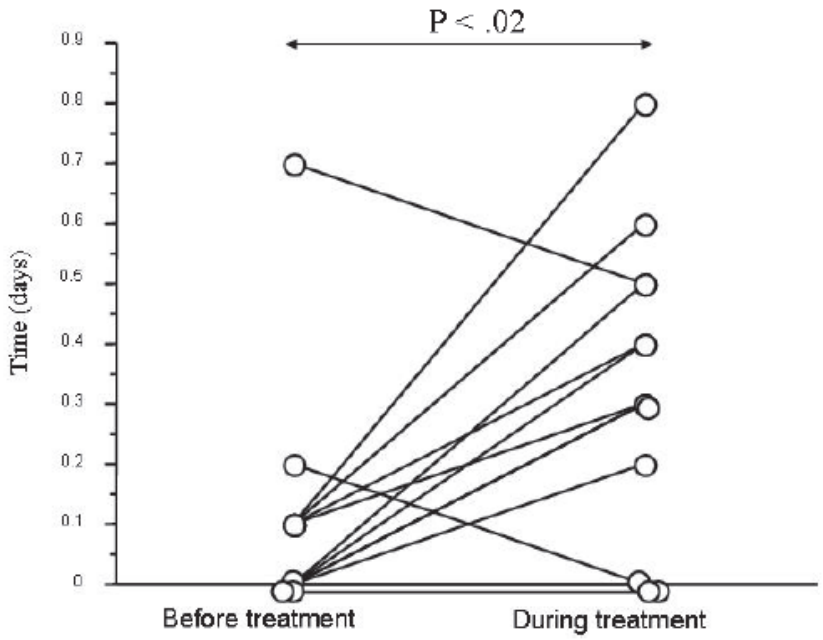
Peleman et al. CG&H 2016

Role of bile acids in IBS diarrhea

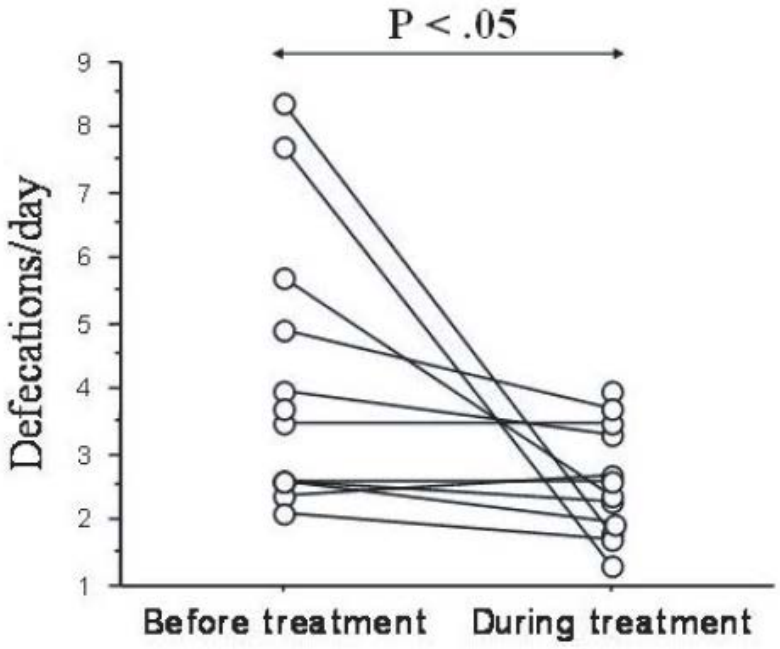


- Malabsortion
- Increased production
- Changes in microbiota
- Colonic hypersensitivity

Effect of cholestyramine in idiopathic BA diarrhea



Segmental transit in the transverse colon



Stool frequency

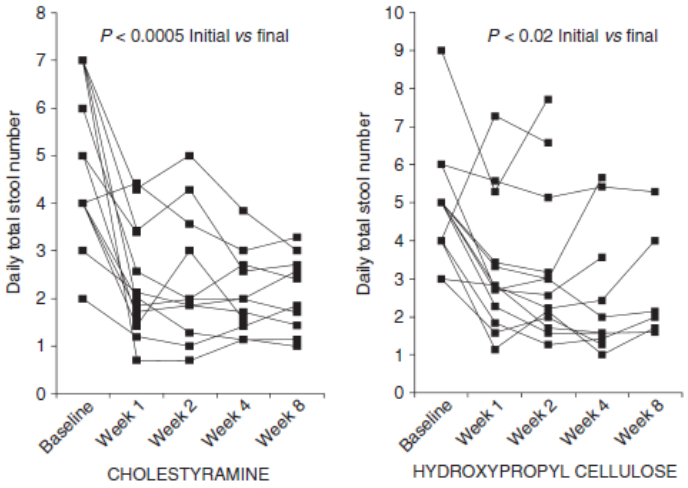
Stotzer et al. Neuroenterolgy 2015

Randomised clinical trial: colestyramine vs. hydroxypropyl cellulose in watery FDr

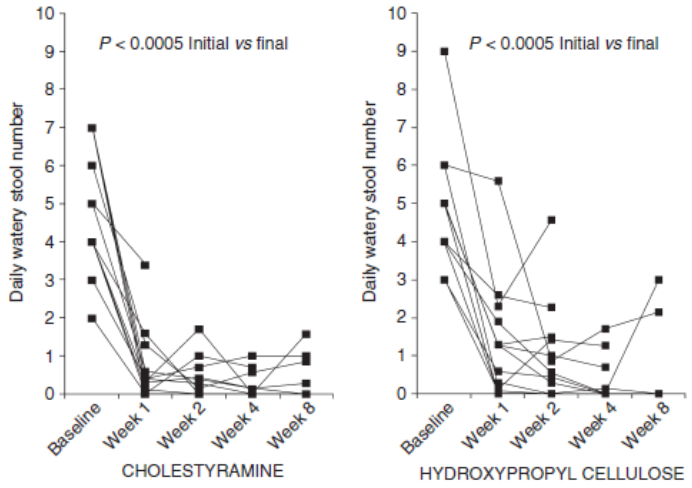
Colestyramine sachets 4 g twice daily (n = 13)

Cellulose sachets twice daily (n = 13)

for 8 weeks



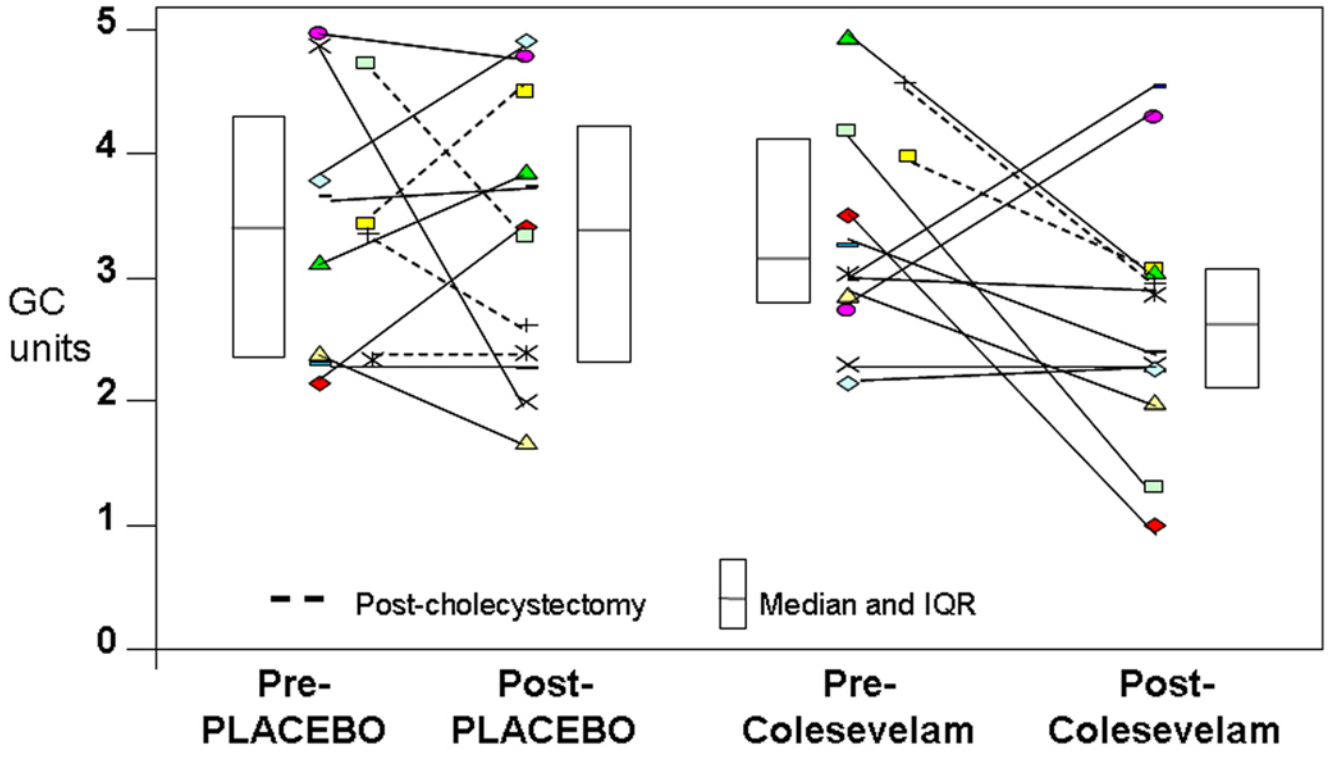
Daily total stool number



Daily watery stool number

Fernández-Bañares et al. APT 2015

Effects of colesevelam on intestinal transit

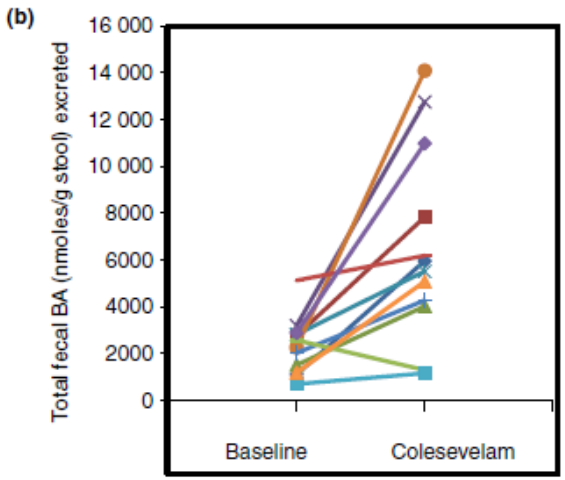


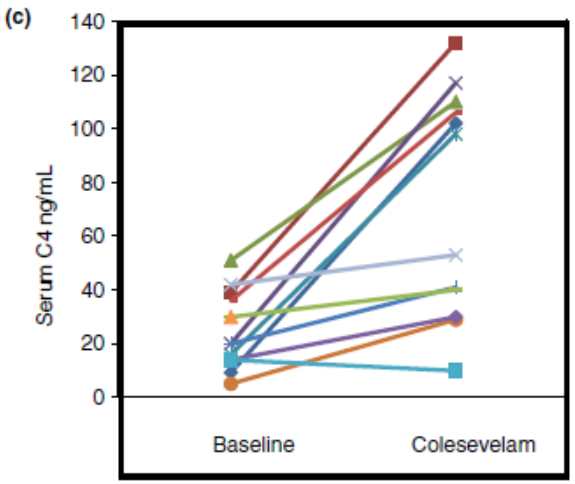
Odunsi-Shiyanbade et al. Clin G&H 2010

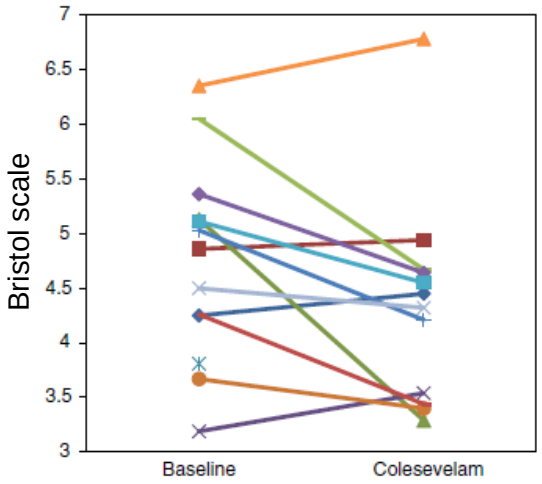
Effects of colesevelam on IBS-D

Colesevelam, 1875 mg [3 tablets (625 mg tablets)] twice daily, for 10 days

- ✓ Total 48-h fecal BA excretion
- ✓ Fasting serum C4 (7a-hydroxy-4-cholesten-3-one)
- ✓ Stool consistency







Camilleri et al. APT 2015

Pharmacogenetics of the effects of colesevelam on colonic transit in IBS-D

FGFR4 rs351855 and KLB rs4975017 SNPs may identify a subset of IBS-D patients with beneficial response to colesevelam.

Wong et al. Dig Dis Sci 2012

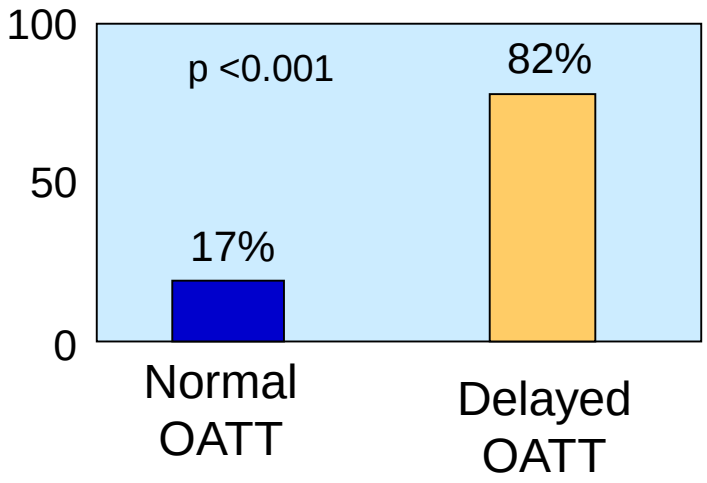
IBS-C & FC: BA synthesis related to colonic transit

Female patients

- **23 IBS-C**
- **4 FC**

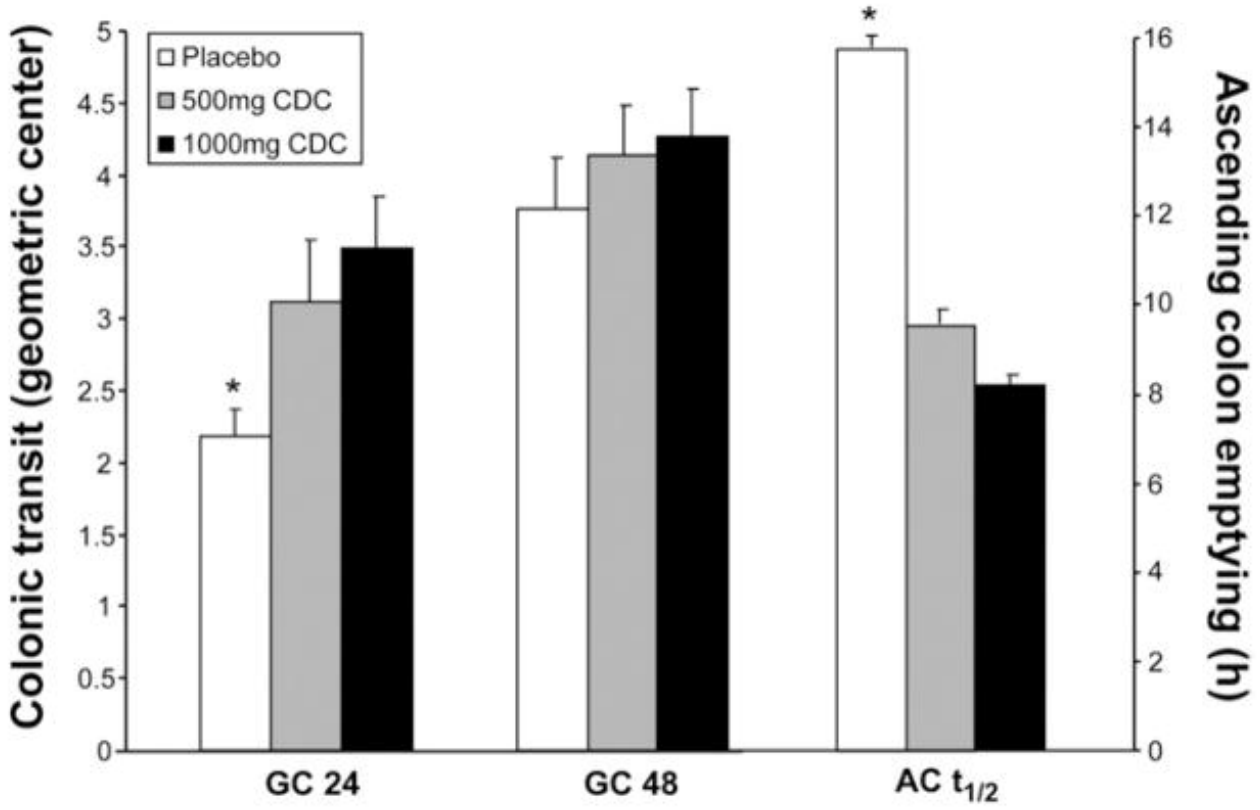
7-alpha-hydroxy-4-cholesten-3-one (C4) levels reflecting BA synthesis at 0800 h and 1300 h

Absence of C4 increase at lunchtime



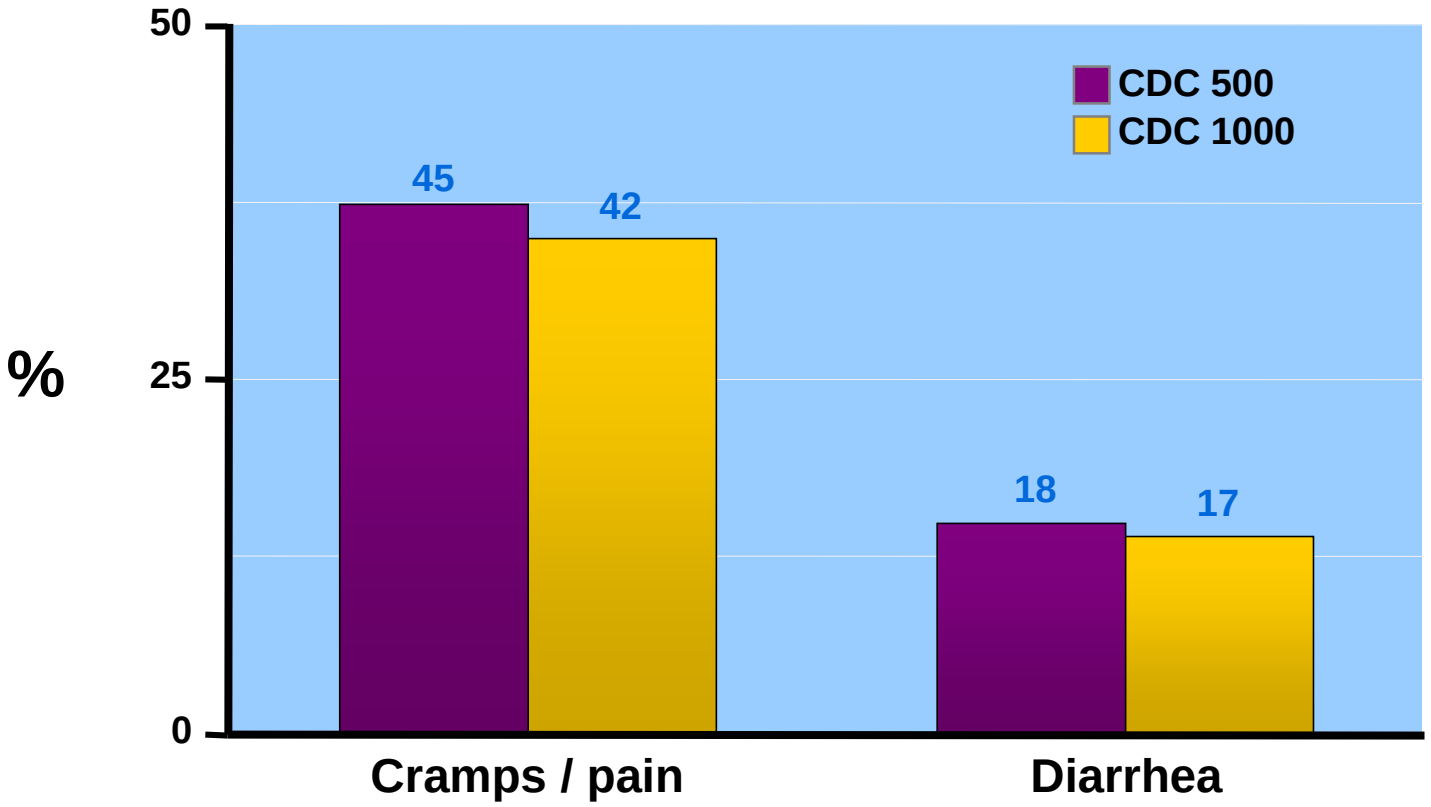
Abrahamsson et al. Scand J Gastro 2008

Chenodeoxycholate in females with IBS-C



Rao et al. Gastroenterology 2010

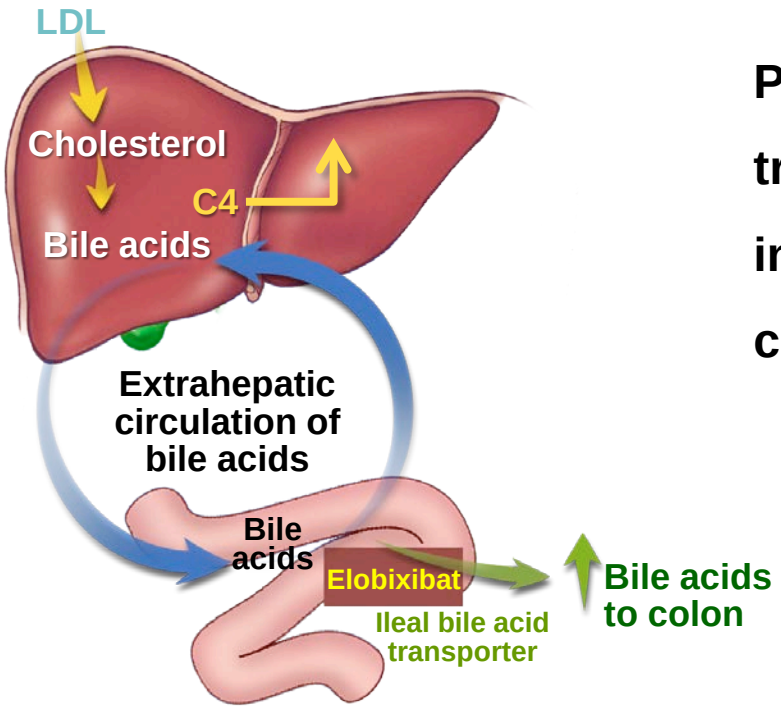
Adverse events of chenodeoxycholate in female patients with IBS-C



- **No placebo patients developed pain or diarrhea**

Rao et al. Gastroenterology 2010

Elobixibat: mechanism of action

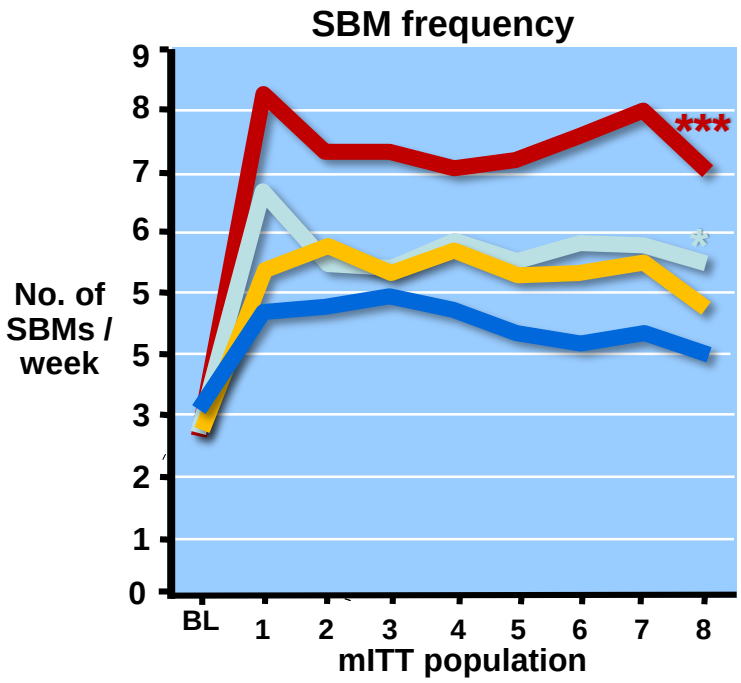


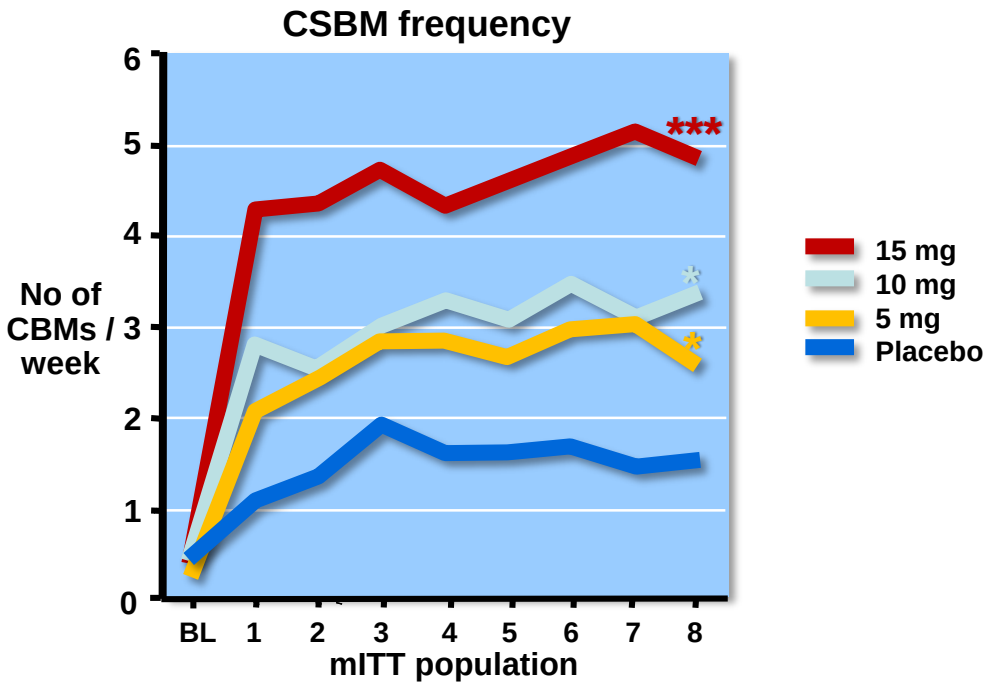
Partially blocks the ileal bile acid transporter from the luminal side, increasing delivery of bile acids to the colon inducing secretion and motility

Decreased bile acid synthesis and bile acid concentration may contribute to the pathogenesis of slow transit constipation (Hofmann, Camilleri)

Chey WD, et al. Am J Gastroenterol 2011; 106:1803
Camilleri M, Am J Gastroenterol 2011; 106(5):835

Effect of Elobixibat on constipation: Results of phase IIb Study





Chey W, et al. Am J Gastroenterol 2011; 106:1803

BA-related diarrhea: something to have in mind

Tissue	Physiological process	Major factors	Other factors
Liver	BA synthesis BA uptake BA conjugation	FXR FGFR4 βKlotho	Other genes MicroRNAs
Gallbladder	BA secretion	Recycling rate CCK	FGF19
Duodenum and jejunum	BA integrity	Bacteria (deconjugation) Motility	Other dietary factors
Ileum	BA reuptake	Ileal mass ASBT, FABP6, OSTα/OSTβ	Inflammatory cytokines Diet1
	FGF19 feedback	FXR FGF19	
Colon	Effects of unabsorbed bile acid	Bacterial metabolism (to DCA/LCA) Anion secretion Colonic motility	Microbiome FXR TGR5
		Overall response	Visceral sensitivity Psychological response