Elobixibat and its potential role in chronic idiopathic constipation

Andres Acosta and Michael Camilleri

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Abstract: Chronic idiopathic constipation is highly prevalent among adults. Bile acids (BAs) and the enterohepatic BA circulation modulate colonic secretion and motility that affect transit. BAs in the colon have a dual action as osmotic and stimulant agents. Newer agents, such as elobixibat (A3309), an inhibitor of the ileal BA transporter, have the potential to improve significantly the management of chronic constipation, with minimal adverse effects. Elobixibat modulates the enterohepatic BA circulation, enhancing the delivery of BAs to the colon where they induce secretory and motor effects. Secondary effects of the inhibition of BA absorption are reduced activation of the farnesoid X receptor, decreased secretion of fibroblast growth factor-19 into the portal circulation, and increased BA synthesis. This review focuses on the role of BAs, the enterohepatic BA circulation, and an ileal BA transporter inhibitor (elobixibat) in chronic constipation.

Keywords: A3309, bile acid transporter, functional constipation, IBS-C

Introduction

Constipation is a syndrome defined by abnormal bowel symptoms that may be primary or secondary to an underlying disorder [Bharucha *et al.* 2013b]. Commonly used criteria differentiate between ‘functional or chronic idiopathic constipation’ (CC) and ‘constipation-predominant irritable bowel syndrome’ (IBS-C), and define CC as two or more of the following for at least 12 weeks in the preceding 6 months: straining, lumpy or hard stools, sensation of incomplete evacuation, sensation of anorectal obstruction/blockade, manual maneuvers to facilitate defecation, and absence of loose stools [Longstreth *et al.* 2006]. CC can be associated with normal colonic transit, slow colonic transit, and/or defecatory disorders [Bharucha *et al.* 2013b; Camilleri, 2012]; it is worth noting that defecatory disorders may also be associated with slow colonic transit [Nullens *et al.* 2012].

The prevalence of CC is 16% in adults overall and almost double that number (33.5%) in people over 60 years of age [Bharucha *et al.* 2013b]. The diagnosis of CC requires a careful history and physical examination, including rectal examination. Organic disorders need to be excluded, especially with recent onset of constipation or alteration of bowel function. Treatment algorithms have been proposed based on consensus

guidelines: for details, refer to the recent American Gastroenterological Association technical review on constipation [Bharucha *et al.* 2013b], and refer to Figure 1 for the diagnostic algorithm [Bharucha *et al.* 2013a]. The prevalence of each subclass of CC varies among different studies. In 1411 patients evaluated by a single gastroenterologist in a tertiary medical center, 960 (68%) patients had normal transit constipation, 61 (4.3%) patients had slow transit constipation, and 390 (27.6%) patients had a defecatory disorder [Nullens *et al.* 2012].

In the case of CC without defecatory disorder, the available medications include: stool softeners (docusate sodium), osmotic agents (sorbitol, lactulose, and polyethylene glycol), stimulants (glycerin, bisacodyl, picosulfate, senna, and cascara), saline laxatives (magnesium), lubricant (mineral oil), oral secretagogues, such as lubiprostone [Drossman *et al.* 2009; Schey and Rao, 2011], and linaclotide [Lembo *et al.* 2011; Andresen *et al.* 2007], 5-HT₄ agonists in several countries other than the USA, for example, prucalopride [Bouras *et al.* 2001; Camilleri *et al.* 2008], and enemas (mineral oil retention enema, tap-water enema, phosphate enema, and soapsuds enema). In spite of the availability of numerous pharmacologic options, up to half of the adults with CC reported that they were not completely satisfied

Correspondence to:

Michael Camilleri, MD
Clinical Enteric
Neuroscience
Translational and
Epidemiological Research
(CENTER), Mayo Clinic,
200 First St SW, Charlton
Building, Room 8–110,
Rochester, MN 55905, USA
camilleri.michael@mayo.edu

Andres Acosta, MD, PhD
Clinical Enteric
Neuroscience
Translational and
Epidemiological Research
(CENTER), Mayo Clinic,
Rochester, MN, USA

Figure 1. Diagnostic algorithm for chronic constipation. (Reproduced with permission from Bharucha *et al.* [2013a].)

with the current treatment options prior to the approval of linaclotide, lubiprostone, and prucalopride [Johanson and Kralstein, 2007], including patients participating in phase III clinical trials of new treatments for CC [e.g. Camilleri *et al.* 2008]. Thus, there is still an unmet need for safe and effective treatments for CC.

Significant advances in understanding the underlying mechanisms of CC have led to novel targets, receptors, neurotransmitters, and fluid and electrolyte secretion and reabsorption. In addition to the approved drugs detailed above, others are in development: prokinetic 5-HT₄ receptor agonists, such as velusetrag and naronapride; guanylyl cyclase C receptor agonists, such as plecanatide; a bile acid (BA) (delayed-release chenodeoxycholic

acid [CDCA]); an ileal BA transporter (IBAT) inhibitor (elobixibat) [Camilleri, 2013].

This review focuses on the role of BAs, the enterohepatic circulation, and the IBAT inhibitor, elobixibat, in CC.

Enterohepatic circulation of BAs

BAs are detergent molecules mainly responsible for fat emulsification, and lipid digestion and absorption in the small intestine. In addition, BAs are versatile molecules with multiple other functions in the gastrointestinal tract, such as antimicrobial activity, modulation of fluid and electrolyte absorption, regulation of epithelial gene expression, growth of intestinal epithelium, and

gastrointestinal motility [Hofmann, 2009]. Primary BAs (cholic acid, CDCA, and ursodeoxycholic acid) are synthesized from cholesterol in the hepatocyte, secreted from the liver predominantly in a conjugated state with glycine and taurine, and, following their pivotal role in fat emulsification and lipid digestion and absorption in the small intestine, they are extensively (95%) reabsorbed through the IBAT (also called the apical sodium-coupled BA transporter). About 5% of BAs pass into the colon where they are deconjugated and dehydroxylated by intestinal bacteria into secondary BAs, deoxycholic acid (DCA) and lithocholic acid (LCA). Thus, the enterohepatic circulation of BAs is the process whereby primary BAs, secreted from the hepatocyte into the

canalicular bile, traverse through the biliary tract into the duodenum, and course through the small bowel until actively absorbed in the terminal ileum, or passively absorbed by diffusion in the colon (Figure 2). Once they reach the portal circulation and are transported to the liver, BAs are taken up into the hepatocytes by specific transporter molecules [Hofmann, 2009].

The enterohepatic circulation of BAs has two regulatory sites that produce negative feedback in BA synthesis. In the hepatocyte, BAs inhibit the function of the farnesoid X receptor (FXR) to induce a short heterodimer protein that activates cholesterol 7 α -hydroxylase (CYP7A1), down-regulating BA biosynthesis [Twisk *et al.* 1995]. In

Figure 2. Enterohepatic bile-acid circulation and synthesis.

the enterocyte, BAs activate FXR to induce the enterocyte to secrete fibroblast growth factor-19 (FGF-19), an analog of FGF-15 in mice, into the portal circulation. FGF-19 binds to fibroblast growth factor receptor 4 (FGFR4). This involves interaction of a separate molecule, klotho β (KLB), on the hepatocyte that leads to the suppression of CYP7A1 expression and decreased BA synthesis [Wong *et al.* 2011a; Jung *et al.* 2007; Cicione *et al.* 2012; Johnston *et al.* 2011].

BAs and gastrointestinal motility

BAs modulate colonic transit by two mechanisms: secretory and prokinetic [Camilleri, 2014]. Thus, BAs increase colonic secretion of water and electrolytes. In 20 healthy volunteers, perfusion of dihydroxy BAs into the colon in concentrations of 3 mM or higher induced dose-related secretion of chloride, sodium, potassium, bicarbonate, and water when compared with an iso-osmolar control electrolyte solution [Mekhjian *et al.* 1971]. In addition, certain BAs are prokinetic in the colon, stimulating high amplitude, propagated contractions. In 10 healthy volunteers, when CDCA, was perfused into the rectum and left colon at 1 mM concentration, it doubled the frequency of propagated contractions [Bampton *et al.* 2002]. These findings on the effects of BAs on colonic motor function were confirmed by two randomized, double-blind trials using a BA sequestrant (colesevelam), which induced slowing of colonic transit in irritable bowel syndrome with diarrhea (IBS-D), whereas CDCA accelerated colonic transit in healthy subjects [Odunsi-Shiyanbade *et al.* 2010], and in patients with IBS-C [Rao *et al.* 2010]. Thus, for example, ileocolonic-release CDCA (IR-CDCA), 500 mg and 1000 mg, was tested in a randomized, double-blind, placebo-controlled study of 36 women with IBS-C. IR-CDCA accelerated colonic transit, induced looser stool consistency, increased stool frequency, and produced greater ease of stool passage when compared with placebo. The most common side effect was lower abdominal cramping and pain in 45% of participants, consistent with the significant stimulation of colonic motility [Rao *et al.* 2010].

Deficiency of FGF-19 produces increased BA synthesis and diarrhea [Walters *et al.* 2009]. In addition, variants in the genes for the proteins involved in the enterohepatic BA circulation may also provide evidence of the potential of BA to modulate colonic motility. Genetic variation in *KLB* (Arg728Gln) is associated with IBS-D and

accelerated colonic transit: the gene variant results in instability of the KLB protein synthesized, resulting in the inability of FGF-19 to reduce hepatocyte BA synthesis [Wong *et al.* 2011a]. *FGFR4* genetic variations alone [Camilleri *et al.* 2014], or by interaction with the *KLB* variations, alter colonic transit [Wong *et al.* 2011a]; in addition, *FGFR4* polymorphisms are also associated with alterations in the colonic transit in response to administered CDCA [Rao *et al.* 2010].

Finally, the G-protein-coupled BA receptor 1 (GPBAR1) is present in enteroendocrine cells and in components of the motor and sensory apparatus of the enteric nervous system [Poole *et al.* 2010]. Expression and function of GPBAR1 are involved in the prokinetic effects of BAs [Aleml *et al.* 2013]; genetic variation in *GPBAR1* was associated with acceleration of small intestinal and colonic transit [Camilleri *et al.* 2011].

BAs and constipation

Individuals with IBS-C have a decreased concentration of secretory unconjugated BA, CDCA, nonsecretory BA, and DCA, when compared with healthy controls or patients with IBS-D (Figure 3) [Shin *et al.* 2013; Wong *et al.* 2012]. The nonsecretory, unconjugated BA, LCA, was the predominant fecal BA when compared with healthy controls in IBS-C [Shin *et al.* 2013]. In addition, there is a positive correlation between stool number and form, colonic transit at 24 h and 48 h, total fecal unconjugated BA, and percentage of primary BAs [Shin *et al.* 2013]. Conversely, there is a negative correlation between colonic transit and percentage of fecal LCA, that is, the slower colonic transit in patients with IBS-C is associated with higher fecal LCA [Shin *et al.* 2013].

Elobixibat

Chemistry, pharmacology, and pharmacokinetics

Elobixibat (A3309) is the pure enantiomer of a synthetically modified 1,5-benzothiazepine, based on a seven-membered heterocyclic ring attached to a benzene ring (chemical formula $C_{36}H_{45}N_3O_7S_2$). It acts locally in the lumen of the gastrointestinal tract by binding to and partially inhibiting IBAT in the ileal mucosa. Elobixibat is highly selective for IBAT, with an affinity more than 450-fold higher than for human liver sodium-dependent BA transporter, and

Figure 3. Individual predominant fecal bile acids in patients with IBS-C and healthy controls. [Data taken from Shin *et al.* [2013].]

IBS-C, constipation-predominant irritable bowel syndrome.

more than 9000-fold higher than for neutral amino-acid transporter [Gillberg, 2010]. Elobixibat increased hepatic BA synthesis in dogs in a dose-dependent manner when compared with controls [Gillberg, 2010].

Elobixibat is minimally absorbed into the circulation after oral administration. The low systemic bioavailability supports elobixibat's mechanism of action as a local inhibitor of IBAT. When absorbed, elobixibat is protein bound (> 99%) in plasma, with a half-life of less than 4 h. Elobixibat inhibits CYP2C9 and CYP3A4. However, since its absorption is so low, there is a low risk of drug-drug interactions as a result of inhibition of the CYP enzyme after oral dosing [Simren *et al.* 2011].

Clinical trials: pharmacodynamics, safety, and efficacy

The effects of elobixibat in CC have been assessed in three published trials to date.

A phase I, randomized, double-blind, placebo-controlled, single-center trial over 14 days focused mainly on safety and tolerability of elobixibat in 30 CC patients in six groups: placebo *versus* elobixibat at doses 0.1 mg, 0.3 mg, 1 mg, 3 mg, and 10 mg [Simren *et al.* 2011]. In addition, colonic transit time (CTT) by radiopaque markers, plasma C4 (a surrogate of the rate of hepatic BA-synthesis rate), and cholesterol levels were assessed. Elobixibat, 10 mg daily, accelerated colonic transit, reducing CTT when compared with placebo. Elobixibat also increased the plasma C4 levels and decreased total cholesterol and low-density lipoprotein (LDL) cholesterol in a dose-dependent manner. These three actions are consistent with the reduced ileal BA absorption in the ileum, reducing the negative feedback of hepatocyte BA synthesis, and therefore shunting steroid synthesis in the hepatocyte from cholesterol and LDL cholesterol to increased BA synthesis.

In a phase IIa, single-center, randomized, double-blind, placebo-controlled trial, 36 women with CC by Rome II criteria were randomized to oral placebo, 15 mg, or 20 mg elobixibat for 14 consecutive days. Colonic transit was measured over 48 h by a validated scintigraphic method. Bowel functions were assessed as secondary endpoints. Biochemical secondary endpoints included serum C4, triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, and LDL cholesterol. Elobixibat accelerated colonic transit, induced looser stool consistency, decreased constipation rating, and reduced straining compared with placebo (Figure 4). The most common side effects were lower abdominal cramping/pain in 36% of participants and 50% of participants on 15 mg and 20 mg, respectively ($p = 0.004$), and diarrhea in 30% of participants receiving the 20 mg dose ($p = \text{not significant}$) [Wong *et al.* 2011b].

In a multicenter, phase IIb, double-blind, placebo-controlled trial, 190 CC patients were randomized to placebo, 5 mg, 10 mg, or 15 mg elobixibat daily for 8 weeks. The primary endpoint was change in the frequency of spontaneous bowel movements (SBMs) per week at week 1 of treatment, compared with baseline. Other bowel function characteristics, plasma C4, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were secondary endpoints. Elobixibat was associated with a significantly greater increase in the number of SBMs per week from baseline to placebo (mean change 4.0 for 10 mg [$p < 0.002$], and 5.4 for 15 mg [$p < 0.001$] elobixibat *versus* 1.7 for

Figure 4. Effect of elobixibat (A3309) and placebo on overall colonic transit at 24 h and 48 hours (left panel), mean $\pm$ standard error of mean by Dunnett's test (each dose *versus* placebo) * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Note acceleration of colonic transit with both A3309 doses. Colonic transit scintiscans at 24 h during baseline, and at 24 h and 48 h on treatment, representative of each of the three groups (right panel, placebo, A3309 15 mg, and A3309 20 mg). Intensity of images reflects the concentration of counts in each region. Note that A3309 accelerates colonic transit relative to placebo. [Reproduced with permission from Wong *et al.* [2011b].]

placebo). The increased SBMs with elobixibat were dose dependent and maintained over the duration of the 8-week treatment period, when compared with placebo (Figure 5). In addition, elobixibat significantly loosened stool consistency and decreased straining during all 8 weeks of treatment compared with placebo, and elobixibat, 15 mg, improved bloating severity, but not abdominal discomfort or pain. The studies reported similar adverse effects described as mild or moderate abdominal cramps or pain (0%, 10%, 11%, and 27% in the placebo, 5 mg, 10 mg, and 15 mg elobixibat, respectively), and diarrhea (2%, 8%, 6%, and 13% in the placebo, 5 mg, 10 mg, and 15 mg elobixibat groups, respectively). There were no severe adverse events [Chey *et al.* 2011].

Currently, two large, multicenter phase III trials, ECHO 1 and ECHO 2, are enrolling patients with a goal to recruit 1700 patients in 200 sites worldwide. The study is intended to demonstrate the efficacy and safety of repeated daily doses of

elobixibat compared with placebo over a period of 26 weeks in the ECHO 1 trial [ClinicalTrials.gov identifier: NCT01827592], and for 12 weeks in the ECHO 2 trial [ClinicalTrials.gov identifier: NCT01833065]. Both trials are expected to be completed by the end of 2014.

Potential role of elobixibat in patients with chronic constipation. The presumed dual action of elobixibat on colonic secretion and motility may be advantageous in the treatment of CC when compared with single-action agents such as osmotic agents, secretagogues, or prokinetics. The dual action may potentially simplify the treatment of patients with constipation with no evidence of a rectal evacuation disorder without having to determine whether the problem is due to normal transit or slow transit constipation. However, formal studies are required to assess the effects of elobixibat on colonic contractility, and on the resolution of symptoms and delayed transit in patients with slow transit constipation before it can be recommended

Figure 5. Change from baseline in weekly SBM frequency for treatment week 1. ITT, intention to treat; SBM, spontaneous bowel movement. (Reproduced with permission from Chey *et al.* [2011].)

in preference to other agents. In fact, the relative efficacy of all these agents in the treatment of slow transit constipation has not been tested.

Theoretical risk of colorectal cancer. A meta-analysis of 20 clinical trials showed increased fecal excretion of the primary BA, CDCA, in patients with colorectal cancer [Tong *et al.* 2008]. However, there is no direct evidence of causation between BAs and the development of colorectal cancer based on epidemiological studies [Haines *et al.* 2000; Little *et al.* 2002; Hill *et al.* 1982], therapeutic studies in patients who received CDCA for several months or years for gallstone dissolution [Iser and Sali, 1981], and in patients after partial ileal bypass performed for hyperlipidemia at 5 years [Buchwald *et al.* 1998], or in 25 years of follow up [Buchwald *et al.* 2010]. Thus, the theoretical colorectal cancer risk with exposure to increased intracolonic BA concentrations needs to be further evaluated, but the current evidence is reassuring. As with all new drug-development programs, meticulous studies including risk management programs will be necessary to exclude potential for colonic carcinogenicity.

Conclusion

Chronic constipation has a high prevalence among adults, and the current treatments do not

meet patients' expectations. Elobixibat, an IBAT inhibitor, modulates the enterohepatic BA circulation, and increases BA synthesis, enhancing the delivery of BAs to the colon to increase colonic motility, and secretion and fecal excretion of BAs. Elobixibat has significant effects on the manifestations of CC, with minimal and tolerable adverse effects.

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Conflict of interest statement

MC served as an advisor (payment to his employer) to Albireo and Ferring Pharmaceuticals for work on elobixibat, and received a research grant from Albireo for work described in Wong *et al.* [2011b].

References

- Alemi, F., Poole, D., Chiu, J., Schoonjans, K., Cattaruzza, F., Grider, J. *et al.* (2013) The receptor TGR5 mediates the prokinetic actions of intestinal bile acids and is required for normal defecation in mice. *Gastroenterology* 144: 145–154.

- Andresen, V., Camilleri, M., Busciglio, I., Grudell, A., Burton, D., McKinzie, S. *et al.* (2007) Effect of 5 days linaclotide on transit and bowel function in females with constipation-predominant irritable bowel syndrome. *Gastroenterology* 133: 761–768.
- Bampton, P., Dinning, P., Kennedy, M., Lubowski, D. and Cook, I. (2002) The proximal colonic motor response to rectal mechanical and chemical stimulation. *Am J Physiol Gastrointest Liver Physiol* 282: G443–G449.
- Bharucha, A., Dorn, S., Lembo, A. and Pressman, A. (2013a) American Gastroenterological Association medical position statement on constipation. *Gastroenterology* 144: 211–217.
- Bharucha, A., Pemberton, J. and Locke, G. (2013b) American Gastroenterological Association technical review on constipation. *Gastroenterology* 144: 218–238.
- Bouras, E., Camilleri, M., Burton, D., Thomforde, G., McKinzie, S. and Zinsmeister, A. (2001) Prucalopride accelerates gastrointestinal and colonic transit in patients with constipation without a rectal evacuation disorder. *Gastroenterology* 120: 354–360.
- Buchwald, H., Rudser, K., Williams, S., Michalek, V., Vagasky, J. and Connett, J. (2010) Overall mortality, incremental life expectancy, and cause of death at 25 years in the program on the surgical control of the hyperlipidemias. *Ann Surg* 251: 1034–1040.
- Buchwald, H., Varco, R., Boen, J., Williams, S., Hansen, B., Campos, C. *et al.* (1998) Effective lipid modification by partial ileal bypass reduced long-term coronary heart disease mortality and morbidity: five-year posttrial follow-up report from the POSCH. Program on the Surgical Control of the Hyperlipidemias. *Arch Intern Med* 158: 1253–1261.
- Camilleri, M. (2012) Peripheral mechanisms in irritable bowel syndrome. *N Engl J Med* 367: 1626–1635.
- Camilleri, M. (2013) Pharmacological agents currently in clinical trials for disorders in neurogastroenterology. *J Clin Invest* 123: 4111–4120.
- Camilleri, M. (2014) Advances in understanding of bile acid diarrhea. *Expert Rev Gastroenterol Hepatol* 8: 49–61.
- Camilleri, M., Kerstens, R., Ryck, A. and Vandeplassche, L. (2008) A placebo-controlled trial of prucalopride for severe chronic constipation. *N Engl J Med* 358: 2344–2354.
- Camilleri, M., Klee, E., Shin, A., Carlson, P., Li, Y., Grover, M. *et al.* (2014) Irritable bowel syndrome-diarrhea: characterization of genotype by exome sequencing, and phenotypes of bile acid synthesis and colonic transit. *Am J Physiol* 306: G13–G26.
- Camilleri, M., Vazquez-Roque, M., Carlson, P., Burton, D., Wong, B. and Zinsmeister, A. (2011) Association of bile acid receptor TGR5 variation and transit in health and lower functional gastrointestinal disorders. *Neurogastroenterol Motil* 23: 995–999.
- Chey, W., Camilleri, M., Chang, L., Rikner, L. and Graffner, H. (2011) A randomized placebo-controlled phase IIb trial of a3309, a bile acid transporter inhibitor, for chronic idiopathic constipation. *Am J Gastroenterol* 106: 1803–1812.
- Cicione, C., Degirolamo, C. and Moschetta, A. (2012) Emerging role of fibroblast growth factors 15/19 and 21 as metabolic integrators in the liver. *Hepatology* 56: 2404–2411.
- Drossman, D., Chey, W., Johanson, J., Fass, R., Scott, C., Panas, R. *et al.* (2009) Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome – results of two randomized, placebo-controlled studies. *Aliment Pharmacol Ther* 29: 329–341.
- Gillberg, P., Dahlstrom, M., Starke, I. and Ostlund-Lindqvist, A. (2010) The IBAT inhibition by A3309 a potential mechanism for the treatment of constipation. *Gastroenterol Clin North Am* 138: S224.
- Haines, A., Hill, M., Thompson, M., Owen, R., Williams, R., Meade, T. *et al.* (2000) A prospective study of faecal bile acids and colorectal cancer. *Eur J Cancer Prev* 9: 317–323.
- Hill, M., Taylor, A., Thompson, M. and Wait, R. (1982) Fecal steroids and urinary volatile phenols in four Scandinavian populations. *Nutr Cancer* 4: 67–73.
- Hofmann, A. (2009) The enterohepatic circulation of bile acids in mammals: form and functions. *Front Biosci (Landmark Ed)* 14: 2584–2598.
- Iser, J. and Sali, A. (1981) Chenodeoxycholic acid: a review of its pharmacological properties and therapeutic use. *Drugs* 21: 90–119.
- Johanson, J. and Kralstein, J. (2007) Chronic constipation: a survey of the patient perspective. *Aliment Pharmacol Ther* 25: 599–608.
- Johnston, I., Nolan, J., Pattni, S. and Walters, J. (2011) New insights into bile acid malabsorption. *Curr Gastroenterol Rep* 13: 418–425.
- Jung, D., Inagaki, T., Gerard, R., Dawson, P., Kliewer, S., Mangelsdorf, D. *et al.* (2007) FXR agonists and FGF15 reduce fecal bile acid excretion in a mouse model of bile acid malabsorption. *J Lipid Res* 48: 2693–2700.
- Lembo, A. and Camilleri, M. (2003) Chronic constipation. *N Engl J Med* 349: 1360–1368.
- Lembo, A., Schneier, H., Shiff, S., Kurtz, C., MacDougall, J., Jia, X. *et al.* (2011) Two randomized trials of linaclotide for chronic constipation. *N Engl J Med* 365: 527–536.
- Little, J., Owen, R., Fernandez, F., Hawtin, P., Hill, M., Logan, R. *et al.* (2002) Asymptomatic colorectal

- neoplasia and fecal characteristics: a case-control study of subjects participating in the Nottingham fecal occult blood screening trial. *Dis Colon Rectum* 45: 1233–1241.
- Longstreth, G., Thompson, W., Chey, W., Houghton, L., Mearin, F. and Spiller, R. (2006) Functional bowel disorders. *Gastroenterology* 130: 1480–1491.
- Mekhjjan, H., Phillips, S. and Hofmann, A. (1971) Colonic secretion of water and electrolytes induced by bile acids: perfusion studies in man. *J Clin Invest* 50: 1569–1577.
- Nullens, S., Nelsen, T., Camilleri, M., Burton, D., Eckert, D., Iturrino, J. *et al.* (2012) Regional colon transit in patients with dys-synergic defaecation or slow transit in patients with constipation. *Gut* 61: 1132–1139.
- Odunsi-Shiyanbade, S., Camilleri, M., McKinzie, S., Burton, D., Carlson, P., Busciglio, I. *et al.* (2010) Effects of chenodeoxycholate and a bile acid sequestrant, colesvelam, on intestinal transit and bowel function. *Clin Gastroenterol Hepatol* 8: 159–165.
- Poole, D., Godfrey, C., Cattaruzza, F., Cottrell, G., Kirkland, J., Pelayo, J. *et al.* (2010) Expression and function of the bile acid receptor GpBAR1 (TGR5) in the murine enteric nervous system. *Neurogastroenterol Motil* 22: 814–e228.
- Rao, A., Wong, B., Camilleri, M., Odunsi-Shiyanbade, S., McKinzie, S., Ryks, M. *et al.* (2010) Chenodeoxycholate in females with irritable bowel syndrome-constipation: a pharmacodynamic and pharmacogenetic analysis. *Gastroenterology* 139: 1549–1558.
- Ravi, K., Bharucha, A., Camilleri, M., Rhoten, D., Bakken, T. and Zinsmeister, A. (2010) Phenotypic variation of colonic motor functions in chronic constipation. *Gastroenterology* 138: 89–97.
- Schey, R. and Rao, S. (2011) Lubiprostone for the treatment of adults with constipation and irritable bowel syndrome. *Dig Dis Sci* 56: 1619–1625.
- Shin, A., Camilleri, M., Vijayvargiya, P., Busciglio, I., Burton, D., Ryks, M. *et al.* (2013) Bowel functions, fecal unconjugated primary and secondary bile acids, and colonic transit in patients with irritable bowel syndrome. *Clin Gastroenterol Hepatol* 11: 1270–1275.
- Simren, M., Bajor, A., Gillberg, P., Rudling, M. and Abrahamsson, H. (2011) Randomised clinical trial: the ileal bile acid transporter inhibitor A3309 *versus* placebo in patients with chronic idiopathic constipation – a double-blind study. *Aliment Pharmacol Ther* 34: 41–50.
- Tong, J., Ran, Z., Shen, J., Fan, G. and Xiao, S. (2008) Association between fecal bile acids and colorectal cancer: a meta-analysis of observational studies. *Yonsei Med J* 49: 792–803.
- Twisk, J., Hoekman, M., Mager, W., Moorman, A., de Boer, P., Scheja, L. *et al.* (1995) Heterogeneous expression of cholesterol 7 α -hydroxylase and sterol 27-hydroxylase genes in the rat liver lobulus. *J Clin Invest* 95: 1235–1243.
- Walters, J., Tasleem, A., Omer, O., Brydon, W., Dew, T. and Le Roux, C. (2009) A new mechanism for bile acid diarrhea: defective feedback inhibition of bile acid biosynthesis. *Clin Gastroenterol Hepatol* 7: 1189–1194.
- Wong, B., Camilleri, M., Carlson, P., Guicciardi, M., Burton, D., McKinzie, S. *et al.* (2011a) A Klotho β variant mediates protein stability and associates with colon transit in irritable bowel syndrome with diarrhea. *Gastroenterology* 140: 1934–1942.
- Wong, B., Camilleri, M., Carlson, P. and McKinzie, S. (2012) Increased bile acid biosynthesis is associated with irritable bowel syndrome with diarrhea. *Clin Gastroenterol Hepatol* 10: 1009–1015.
- Wong, B., Camilleri, M., McKinzie, S., Burton, D., Graffner, H. and Zinsmeister, A. (2011b) Effects of A3309, an ileal bile acid transporter inhibitor, on colonic transit and symptoms in females with functional constipation. *Am J Gastroenterol* 106: 2154–2164.