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**Inhibition of ileal bile acid transporter: An emerging therapeutic strategy for chronic idiopathic constipation**

Mosińska P *et al.* Inhibition of ileal bile acid transporter

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**Abstract**

Chronic idiopathic constipation (CIC) is a common disorder of the gastrointestinal tract, which encompasses a wide profile of symptoms. Current treatment options for CIC are of limited value; therefore a novel strategy is necessary with an increased effectiveness and safety. Recently, the inhibition of ileal bile acid (BA) transporter has become a promising target for constipation–associated diseases. Through enhanced delivery of BAs into the colon, an accelerated colonic transit, increased stool frequency and relief of constipation–related symptoms are achieved. This article provides an insight into the mechanism of action of ileal BA transporter inhibitors and discusses their potential clinical use for pharmacotherapy of constipation in CIC.

**Key words:** Bile acids; Chronic idiopathic constipation; Ileal bile acid transporter

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**Core tip:** Increasing delivery of bile acids to the colon is considered as one of the most promising approaches for patients with constipation. In this review we discuss recent advances in the field of inhibitors of bile acids transporters and future perspectives in their clinical use.

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**INTRODUCTION**

Chronic idiopathic constipation (CIC) and constipation-predominant irritable bowel syndrome (IBS-C) are common motility disorders of the lower gastrointestinal (GI) tract. The occurrence of CIC ranges between 2%–28% of the population worldwide[1]. In contrast, the overall prevalence of IBS is estimated at approximately 12%–20%[2,3]. CIC and IBS are more commonly reported among woman rather than man; however, functional constipation appears to become more frequent with age, and is primarily found in patients over 65, while IBS mostly affects people younger than 50 years of age.

The symptoms of CIC and IBS–C are diverse; however, a wide range of GI symptoms in CIC overlap with those reported by IBC–C patients and include bloating, infrequent bowel movements (BMs) and abdominal pain and/or discomfort[4-6]. Additionally, recent studies demonstrate that incomplete emptying, painful defecation, straining, hard and lumpy stools are the chief complaints among CIC patients[1,7]. Of note, the major factors distinguishing between CIC and IBS-C are the severity and nature of abdominal pain[5]. Although the symptoms of CIC and IBS-C are not life–threatening, their chronic nature may cause considerable morbidity and can deteriorate patient’s quality of life.

Currently available pharmacological treatments for CIC and IBS-C are directed mainly towards increasing faecal residue and stimulating colon activity, and include Laxatives, Prokinetics, Secretagogues and BA modulators (Table 1).

Consequently, reduced visceral sensitivity/ pain and improved peristalsis in the upper and lower tract are observed[2,26,29-31]. Unfortunately, these treatment options are often of limited efficacy and–according to Johanson *et al[*32]- approximately 50% of patients are not satisfied enough with their constipation therapies. Thereby a novel therapeutic strategy is urgently needed. Increasing delivery of bile acids (BA) to the colon is considered as one of the most promising approach for patients with constipation[33].

**ILEAL BILE ACID TRANSPORTER AS PHARMACOLOGICAL TARGET IN CONSTIPATION**

BAs are synthesized in the liver through hydroxylation and conjugation of cholesterol to chenodeoxycholic acids (CDCA) and cholic acid. Their biosynthetic pathway includes a series of enzymatic conversions initiated by cholesterol–7α–hydroxylase (CYP6A1), which simultaneously constitutes a rate–limiting factor (Figure 1). The rate of hepatic BA synthesis in humans is reflected by the measurement of serum concentrations of a nonspecific marker 7α–hydroxyl–4–cholesten–3–one (C4)[11].

Enterohepatic circulation (EHC) is an important mechanism responsible for the movement of BA molecules from the liver to the small intestine and back to the liver. EHC of BAs depends on absorption of BA in the terminal ileum and colon. Once synthesized, BAs are secreted from the hepatocytes into the canalicular tube and traverse through the biliary tract into the intestine, where they play a crucial role in absorption and solubilisation of cholesterol, dietary lipids and fat–soluble vitamins [36]. Some BAs are reabsorbed by passive mechanism, mostly in the upper intestine. However, almost 95% are reclaimed by the ileal bile acid transporter (IBAT or apical sodium–dependent BA transporter, ASBT), abundantly expressed in terminal ileum[8,10,33,36]. This sodium– and potential–driven transporter reabsorbs BAs from the lumen of the intestine through the apical brush border membrane[12]. This mechanism is considered as a major determinant of BA pool size in the human body and is an essential regulator of the lipid and cholesterol homeostasis. BAs are then recycled back *via* portal vein into the liver for their re-secretion into bile, which constitutes the finishing step of the EHC.

Equilibrium between BA synthesis, secretion and intestinal re–absorption is vital for the maintenance of important physiological processes, especially in case of colonic secretion and motility. Wong *et al[*11] found a correlation between BA synthesis and constipation, which results from the reduction of hepatic BA synthesis and lower stool BA excretion. Furthermore, mutations in the IBAT gene (Slc10a2) contributing to the disruption of EHC cause BA malabsorption, in which congenital diarrhea, steatorrhea and low level of plasma cholesterol are present[12,13]. The same effect of malabsorption was also observed in IBAT knockout mice[12]. Hence, a number of studies targeted the impaired IBAT reabsorption due to its role in colonic transit and its considerable contribution to the effectiveness of the treatment of constipation[11].

Inhibition of IBAT results in a reduction of ileal BAs reabsorption, therefore the concentration of BAs in the proximal colon is increased, similarly to the infusion of both, conjugated and non–conjugated BAs into the colon. This promotes intracolonic secretion via several mechanisms, including intracellular activation of secretory mechanisms *e.g.,* adenylate cyclase, enhancement of mucosal permeability[14], and inhibition of apical Cl-/OH- exchange[15]. A study by Bampton *et al[*16] revealed a twofold increase in proximal colonic propagating sequence frequency in healthy volunteers after administration of 1 mmol of CDCA. Moreover, administration of CDCA in patients with chronic constipation, at dosages of 750 - 1000 mg per day, resulted in an increase of BMs, decrease in stool consistency and shortened period of faecal excretion[18,20]. Treatment with sodium chenodeoxycholate at low dosage of 0.5 - 1.0 g/d also ameliorated colonic transit, and enabled frequent defecation in healthy volunteers and patients with ailments related to constipation[18,20]. Finally, it has been suggested that high luminal accumulation of selected BAs may produce a laxative effect, generally by the stimulation its prosecretory and pro-motility actions[8,11,33,38].

**CURRENTLY AVAILABLE IBAT INHIBITORS**

Elobixibat (former name: A3309) is a novel and promising approach in the treatment of constipation. Elobixibat inhibits ileal bile acid re–uptake *via* the inhibition of IBAT; during this process, the hepatic synthesis of BA is upregulated on account of the maintenance of EHC homeostasis. Interestingly, the abundant synthesis of cholesterol derivatives leads to the depletion of cholesterol stores in the liver, which simultaneously stimulates the expression of low–density lipoprotein (LDL) receptors on hepatocytes and reduces the level of serum LDL[37].

A recent phase I, randomised showed acceleration of colonic transit, reduction of plasma cholesterol by 11% and 16% in LDL concentration, and an increase in the plasma C4 levels in CIC patients after 14 days of treatment with 10 mg of elobixibat. Moreover, double–blind, placebo–controlled, single–center, clinical trial conducted by Simren *et al[*39], no side effects were registered after its administration. It was suggested that a higher dose of elobixibat may be incorporated into the treatment; however, an overdose of elobixibat may lead to an excessive colonic motility resulting in diarrhea.

Similar favourable therapeutic effects of elobixibat, administered orally for 14 d, were shown by Wong *et al[*37] in a phase IIa, single–center, randomized, double–blind, placebo–controlled trial. An overall colonic transit in CIC patients was significantly accelerated at 24 and 48h in comparison with placebo group. Both doses tested, 15 and 20 mg, were well tolerated and produced alteration in stool consistency, ease of passage and straining, and an increase in the frequency of spontaneous bowel movements, but no increase in stool frequency. No significant ameliorations were detected regarding abdominal bloating and discomfort. After the treatment with elobixibat, only 4/11 patients in the 15 mg group, and 6/12 patients in the 20 mg group experienced mild to moderate abdominal cramps and pain.

A recent placebo–controlled, phase II b clinical trial in 190 CIC patients evaluated the efficacy and safety of elobixibat at three doses[38]. IBAT inhibitor at 10 and 15, but not 5 mg significantly increased BMs and led to an alleviation of constipation–associated symptoms, *i.e.,* straining, bloating and increased stool consistency. The majority of patients in the 10 and 15 mg groups manifested increase in bowel movements within 24 h of initial treatment. Moreover, the effect of elobixibat was maintained up to 8 weeks after administration. As expected, an increased 7α–hydroxy–4–cholesten–3–one (C4) value, which is an intermediate plasma marker in BA synthesis, was documented. Furthermore, consistent with increased BA synthesis the total plasma and LDL cholesterol levels were diminished[38]. It was also revealed that the most common side effects, such as abdominal pain/discomfort and diarrhea, were associated most commonly with 15–mg dosing group. Moreover, the 10 mg dose of elobixibat offered the best efficacy to safety ratio, which may be suited for individual treatment in functional constipation. Interestingly, three large, randomized, multicenter phase III trials, ECHO1 (ClinicalTrials.gov identifier: NCT01827592), ECHO2 (ClinicalTrials.gov identifier: NCT01833065) and ECHO3 (ClinicalTrials.gov identifier: NCT01895543), are anticipated to assess the safety and efficacy of elobixibat within a period of 26, 12 and 52 wk, respectively, with the outcomes expected to appear by the end of 2014. Overall, long–term beneficial effects in patients with CIC need to be evaluated and further studies designed to address the potential of elobixibat are warranted.

**CONCLUSION AND FURTHER PERSPECTIVES**

Inhibition of IBAT constitutes a promising novel approach in the treatment of constipation. The only IBAT inhibitor currently available, elobixibat, exerts prokinetic and prosecretory effects in the colon by enhanced BA synthesis and has been proven effective in CIC patients[40]. The applicability of elobixibat in IBS-C remains questionable and its effects on sensory symptoms still require additional investigation.

Of note, a large body of data indicate that fecal levels of secondary BAs are significantly greater among patients with colorectal adenomata and colorectal cancer (CC)[40-42]. Moreover, it was shown that DCA and LCA may indirectly promote carcinogenesis by modulating intracellular signaling, *e.g.,* induction of cyclooxygenase–2 (COX–2), secretion of matrix metalloproteinase 2 (MMP–2) or activation of plasma membrane muscarinic and EGF receptors that lead to alterations in gene expression and stimulate colon cancer proliferation[43,44]. Exposure of rodent colonic mucosa cells or human adenocarcinoma cell lines, such as HCT–116 and CaCo–2 to BAs stimulates ROS production, which consequently can result in gene mutation and constitutive activation of pro–survival stress–response pathways[45]. In line, DCA administration in a rat model of colonic carcinogenesis enhances the incidence of K–ras point mutation and proliferation in colon tumors[46]. Additionally, Qiao *et al[*47] showed the correlation between tumor–promoting bile acid DCA and the tumor suppressor gene p53, resulting in the inhibition of p53 response to genotoxic compounds in the colon, which ultimately enhance mutagenesis and can increase the risk of cancer. An investigation by Little *et al[*48] , which was based on subjects with asymptomatic cancer and adenomatous polyps, found a relationship between an increased concentration of major BAs and villus adenomas; nonetheless, the risk of large adenomas or colorectal cancer did not correlate with elevated fecal BAs concentration. Similar outcomes were obtained in a cohort study by Haines *et al*[49] where statistical analysis showed no significant differences between the left-sided bowel cancer and control group for any of the concentrations of individual BAs, total BA concentrations, faecal neutral steroids, percentage bacterial conversion and the ratio of LA to DCA concentrations. A weak correlation between CDCA in feces and the risk of right-sided bowel cancer were reported; however, it was postulated that other factors *e.g.,* genetic predisposition were also involved in the causation of large bowel cancer.

Because elobixibat is a relatively new drug and only a limited number of studies are available, thus in order to comprehensively evaluating the risk and benefit profiles of this IBAT inhibitor a meta–analysis is desirable, especially in terms of cancer related–issues and possibility of treatment of IBS–C. On the other hand, development of novel IBAT inhibitors with a modified pharmacological profile and bioavailability could provide drug candidates with favorable endpoint and no adverse effects. Yet another possibility is to encourage the research on other signaling pathways that involve a distinct BA transporter, which is not involved in tumor progression.

To conclude, further meticulous studies are needed to facilitate the development of ultimate chemoprotective strategies for the treatment of constipation.

**REFERENCES**

1 **Shahid S**, Ramzan Z, Maurer AH, Parkman HP, Fisher RS. Chronic idiopathic constipation: more than a simple colonic transit disorder. *J Clin Gastroenterol* 2012; **46**: 150-154 [PMID: 22011587 DOI: 10.1097/MCG.0b013e318231fc64]

2 **Dai C**, Zheng CQ, Jiang M, Ma XY, Jiang LJ. Probiotics and irritable bowel syndrome. *World J Gastroenterol* 2013; **19**: 5973-5980 [PMID: 24106397 DOI: 10.3748/wjg.v19.i36.5973]

3 **Lovell RM**, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. *Clin Gastroenterol Hepatol* 2012; **10**: 712-721.e4 [PMID: 22426087 DOI: 10.1016/j.cgh.2012.02.029]

4 **Andresen V**, Camilleri M, Busciglio IA, Grudell A, Burton D, McKinzie S, Foxx-Orenstein A, Kurtz CB, Sharma V, Johnston JM, Currie MG, Zinsmeister AR. Effect of 5 days linaclotide on transit and bowel function in females with constipation-predominant irritable bowel syndrome. *Gastroenterology* 2007; **133**: 761-768 [PMID: 17854590 DOI: 53827]

5 **Frissora CL**, Koch KL. Symptom overlap and comorbidity of irritable bowel syndrome with other conditions. *Curr Gastroenterol Rep* 2005; **7**: 264-271 [PMID: 16042909 DOI: 10.1007/s11894-005-0018-9]

6 **Liu J**, Hou X. A review of the irritable bowel syndrome investigation on epidemiology, pathogenesis and pathophysiology in China. *J Gastroenterol Hepatol* 2011; **26** Suppl **3**: 88-93 [PMID: 21443718 DOI: 10.1111/j.1440-1746.2011.06641.x]

7 **Schoenfeld PS**. New treatment option for irritable bowel syndrome with constipation and chronic idiopathic constipation. *Gastroenterol Hepatol (N Y)* 2012; **8**: 825-828 [PMID: 24693271]

8 **Bajor A**, Gillberg PG, Abrahamsson H. Bile acids: short and long term effects in the intestine. *Scand J Gastroenterol* 2010; **45**: 645-664 [PMID: 20334475 DOI: 10.3109/00365521003702734]

9 **Mozaffari S**, Nikfar S, Abdollahi M. The safety of novel drugs used to treat irritable bowel syndrome. *Expert Opin Drug Saf* 2014; **13**: 625-638 [PMID: 24669839 DOI: 10.1517/14740338.2014.902932]

10 **Trauner M**, Boyer JL. Bile salt transporters: molecular characterization, function, and regulation. *Physiol Rev* 2003; **83**: 633-671 [PMID: 12663868 DOI: 10.1152/physrev.00027.2002]

11 **Wong BS**, Camilleri M, Carlson P, McKinzie S, Busciglio I, Bondar O, Dyer RB, Lamsam J, Zinsmeister AR. Increased bile acid biosynthesis is associated with irritable bowel syndrome with diarrhea. *Clin Gastroenterol Hepatol* 2012; **10**: 1009-15.e3 [PMID: 22610000 DOI: 10.1016/j.cgh.2012.05.006]

12 **Dawson PA**, Haywood J, Craddock AL, Wilson M, Tietjen M, Kluckman K, Maeda N, Parks JS. Targeted deletion of the ileal bile acid transporter eliminates enterohepatic cycling of bile acids in mice. *J Biol Chem* 2003; **278**: 33920-33927 [PMID: 12819193 DOI: 10.1074/jbc.M306370200]

13 **Jung D**, Fantin AC, Scheurer U, Fried M, Kullak-Ublick GA. Human ileal bile acid transporter gene ASBT (SLC10A2) is transactivated by the glucocorticoid receptor. *Gut* 2004; **53**: 78-84 [PMID: 14684580 DOI: 10.1136/gut.53.1.78]

14 **Raimondi F**, Santoro P, Barone MV, Pappacoda S, Barretta ML, Nanayakkara M, Apicella C, Capasso L, Paludetto R. Bile acids modulate tight junction structure and barrier function of Caco-2 monolayers via EGFR activation. *Am J Physiol Gastrointest Liver Physiol* 2008; **294**: G906-G913 [PMID: 18239063 DOI: 10.1152/ajpgi.00043.2007]

15 **Alrefai WA**, Saksena S, Tyagi S, Gill RK, Ramaswamy K, Dudeja PK. Taurodeoxycholate modulates apical Cl-/OH- exchange activity in Caco2 cells. *Dig Dis Sci* 2007; **52**: 1270-1278 [PMID: 17387613 DOI: 10.1007/s10620-006-9090-8]

16 **Bampton PA**, Dinning PG, Kennedy ML, Lubowski DZ, Cook IJ. The proximal colonic motor response to rectal mechanical and chemical stimulation. *Am J Physiol Gastrointest Liver Physiol* 2002; **282**: G443-G449 [PMID: 11841994 DOI: 10.1152/ajpgi.00194.2001]

17 **Gonzalez-Martinez MA**, Ortiz-Olvera NX, Mendez-Navarro J. Novel pharmacological therapies for management of chronic constipation. *J Clin Gastroenterol* 2014; **48**: 21-28 [PMID: 24172177 DOI: 10.1097/01.mcg.0000436440.05887.02]

18 **Rao AS**, Wong BS, Camilleri M, Odunsi-Shiyanbade ST, McKinzie S, Ryks M, Burton D, Carlson P, Lamsam J, Singh R, Zinsmeister AR. Chenodeoxycholate in females with irritable bowel syndrome-constipation: a pharmacodynamic and pharmacogenetic analysis. *Gastroenterology* 2010; **139**: 1549-158, 1558.e1 [PMID: 20691689 DOI: 10.1053/j.gastro.2010.07.052]

19 **Sood R**, Ford AC. Linaclotide: new mechanisms and new promise for treatment in constipation and irritable bowel syndrome. *Ther Adv Chronic Dis* 2013; **4**: 268-276 [PMID: 24179669 DOI: 10.1177/2040622313500110]

20 **Odunsi-Shiyanbade ST**, Camilleri M, McKinzie S, Burton D, Carlson P, Busciglio IA, Lamsam J, Singh R, Zinsmeister AR. Effects of chenodeoxycholate and a bile acid sequestrant, colesevelam, on intestinal transit and bowel function. *Clin Gastroenterol Hepatol* 2010; **8**: 159-165 [PMID: 19879973 DOI: 10.1016/j.cgh.2009.10.020]

21**Lembo AJ,** Cremonini F, Meyers N, Hickling R. Clinical trial: renzapride treatment of women with irritable bowel syndrome and constipation - a double-blind, randomized, placebo-controlled, study. *Aliment Pharmacol Ther* 2010; **31**: 979-990 [DOI: 10.1111/j.1365-2036.2008.03649.x]

22 **Spiller RC**, Meyers NL, Hickling RI. Identification of patients with non-d, non-C irritable bowel syndrome and treatment with renzapride: an exploratory, multicenter, randomized, double-blind, placebo-controlled clinical trial. *Dig Dis Sci* 2008; **53**: 3191-3200 [PMID: 18465239 DOI: 10.1007/s10620-008-0295-x]

23 **Manini ML**, Camilleri M, Goldberg M, Sweetser S, McKinzie S, Burton D, Wong S, Kitt MM, Li YP, Zinsmeister AR. Effects of Velusetrag (TD-5108) on gastrointestinal transit and bowel function in health and pharmacokinetics in health and constipation. *Neurogastroenterol Motil* 2010; **22**: 42-9, e7-8 [PMID: 19691492 DOI: 10.1111/j.1365-2982.2009.01378.x]

24 **Goldberg M**, Li YP, Johanson JF, Mangel AW, Kitt M, Beattie DT, Kersey K, Daniels O. Clinical trial: the efficacy and tolerability of velusetrag, a selective 5-HT4 agonist with high intrinsic activity, in chronic idiopathic constipation - a 4-week, randomized, double-blind, placebo-controlled, dose-response study. *Aliment Pharmacol Ther* 2010; **32**: 1102-1112 [PMID: 21039672 DOI: 10.1111/j.1365-2036.2010.04456.x]

25 **Camilleri M**, Vazquez-Roque MI, Burton D, Ford T, McKinzie S, Zinsmeister AR, Druzgala P. Pharmacodynamic effects of a novel prokinetic 5-HT receptor agonist, ATI-7505, in humans. *Neurogastroenterol Motil* 2007; **19**: 30-38 [PMID: 17187586 DOI: 10.1111/j.1365-2982.2006.00865.x]

26 **Tillisch K**, Chang L. Diagnosis and treatment of irritable bowel syndrome: state of the art. *Curr Gastroenterol Rep* 2005; **7**: 249-256 [PMID: 16042907 DOI: 10.1007/s11894-005-0016-y]

27 **Foxx-Orenstein AE**, McNally MA, Odunsi ST. Update on constipation: one treatment does not fit all. *Cleve Clin J Med* 2008; **75**: 813-824 [PMID: 19068963 DOI: 10.3949/ccjm.75.11.813]

28 **Chang FY**. Irritable bowel syndrome: the evolution of multi-dimensional looking and multidisciplinary treatments. *World J Gastroenterol* 2014; **20**: 2499-2514 [PMID: 24627587 DOI: 10.3748/wjg.v20.i10.2499]

29 **Arebi N**, Kalli T, Howson W, Clark S, Norton C. Systematic review of abdominal surgery for chronic idiopathic constipation. *Colorectal Dis* 2011; **13**: 1335-1343 [PMID: 20969711 DOI: 10.1111/j.1463-1318.2010.02465.x]

30 **Blackshaw LA**, Brierley SM. Emerging receptor target in the pharmacotherapy of irritable bowel syndrome with constipation. *Expert Rev Gastroenterol Hepatol* 2013; **7**: 15-19 [PMID: 23859756 DOI: 10.1586/17474124.2013.820045]

31 **Wagstaff AJ**, Frampton JE, Croom KF. Tegaserod: a review of its use in the management of irritable bowel syndrome with constipation in women. *Drugs* 2003; **63**: 1101-1120 [PMID: 12749744 DOI: 0012-6667/03/0011-1101/S33.00/0]

32 **Johanson JF**, Kralstein J. Chronic constipation: a survey of the patient perspective. *Aliment Pharmacol Ther* 2007; **25**: 599-608 [PMID: 17305761 DOI: 10.1111/j.1365-2036.2006.03238.x]

33 **Maneerattanaporn M**, Chey WD. Targeting bile acids in the treatment of constipation. *Expert Rev Gastroenterol Hepatol* 2011; **5**: 657-659 [PMID: 22017692 DOI: 10.1586/egh.11.63]

34 **Li T**, Chiang JY. Nuclear receptors in bile acid metabolism. *Drug Metab Rev* 2013; **45**: 145-155 [PMID: 23330546 DOI: 10.3109/03602532.2012.740048]

35 **Pattni S**, Walters JR. Recent advances in the understanding of bile acid malabsorption. *Br Med Bull* 2009; **92**: 79-93 [PMID: 19900947 DOI: 10.1093/bmb/ldp032]

36 **Reshetnyak VI**. Physiological and molecular biochemical mechanisms of bile formation. *World J Gastroenterol* 2013; **19**: 7341-7360 [PMID: 24259965 DOI: 10.3748/wjg.v19.i42.7341]

37 **Wong BS**, Camilleri M, McKinzie S, Burton D, Graffner H, Zinsmeister AR. Effects of A3309, an ileal bile acid transporter inhibitor, on colonic transit and symptoms in females with functional constipation. *Am J Gastroenterol* 2011; **106**: 2154-2164 [PMID: 21876564 DOI: 10.1038/ajg.2011.285]

38 **Chey WD**, Camilleri M, Chang L, Rikner L, Graffner H. A randomized placebo-controlled phase IIb trial of a3309, a bile acid transporter inhibitor, for chronic idiopathic constipation. *Am J Gastroenterol* 2011; **106**: 1803-1812 [PMID: 21606974 DOI: 10.1038/ajg.2011.162]

39 **Simrén M**, Bajor A, Gillberg PG, Rudling M, Abrahamsson H. Randomised clinical trial: The ileal bile acid transporter inhibitor A3309 vs. placebo in patients with chronic idiopathic constipation--a double-blind study. *Aliment Pharmacol Ther* 2011; **34**: 41-50 [PMID: 21545606 DOI: 10.1111/j.1365-2036.2011.04675.x]

40 **Acosta A**, Camilleri M. Elobixibat and its potential role in chronic idiopathic constipation. *Therap Adv Gastroenterol* 2014; **7**: 167-175 [PMID: 25057297 DOI: 10.1177/1756283X14528269]

41 **Ochsenkühn T**, Bayerdörffer E, Meining A, Schinkel M, Thiede C, Nüssler V, Sackmann M, Hatz R, Neubauer A, Paumgartner G. Colonic mucosal proliferation is related to serum deoxycholic acid levels. *Cancer* 1999; **85**: 1664-1669 [PMID: 10223558 DOI: 10.1002/(SICI)1097-0142(19990415)85: 8<1664: : AID-CNCR4>3.0.CO; 2-O]

42 **Tong JL**, Ran ZH, Shen J, Fan GQ, Xiao SD. Association between fecal bile acids and colorectal cancer: a meta-analysis of observational studies. *Yonsei Med J* 2008; **49**: 792-803 [PMID: 18972600 DOI: 10.3349/ymj.2008.49.5.792]

43 **Cheng K**, Raufman JP. Bile acid-induced proliferation of a human colon cancer cell line is mediated by transactivation of epidermal growth factor receptors. *Biochem Pharmacol* 2005; **70**: 1035-1047 [PMID: 16139803 DOI: 10.1016/j.bcp.2005.07.023]

44 **Raufman JP**, Cheng K, Zimniak P. Activation of muscarinic receptor signaling by bile acids: physiological and medical implications. *Dig Dis Sci* 2003; **48**: 1431-1444 [PMID: 12924634]

45 **Payne CM**, Weber C, Crowley-Skillicorn C, Dvorak K, Bernstein H, Bernstein C, Holubec H, Dvorakova B, Garewal H. Deoxycholate induces mitochondrial oxidative stress and activates NF-kappaB through multiple mechanisms in HCT-116 colon epithelial cells. *Carcinogenesis* 2007; **28**: 215-222 [PMID: 16887864 DOI: 10.1093/carcin/bgl139]

46 **Narahara H**, Tatsuta M, Iishi H, Baba M, Uedo N, Sakai N, Yano H, Ishiguro S. K-ras point mutation is associated with enhancement by deoxycholic acid of colon carcinogenesis induced by azoxymethane, but not with its attenuation by all-trans-retinoic acid. *Int J Cancer* 2000; **88**: 157-161 [PMID: 11004662 DOI: 10.1002/1097-0215(20001015)88]

47 **Qiao D**, Gaitonde SV, Qi W, Martinez JD. Deoxycholic acid suppresses p53 by stimulating proteasome-mediated p53 protein degradation. *Carcinogenesis* 2001; **22**: 957-964 [PMID: 11375905 DOI: 10.1093/carcin/22.6.957]

48 **Little J**, Owen RW, Fernandez F, Hawtin PG, Hill MJ, Logan RF, Thompson MH, Hardcastle JD. Asymptomatic colorectal neoplasia and fecal characteristics: a case-control study of subjects participating in the nottingham fecal occult blood screening trial. *Dis Colon Rectum* 2002; **45**: 1233-1241 [PMID: 12352242 DOI: 10.1007/s10350-004-6398-3]

49 **Haines A**, Hill MJ, Thompson MH, Owen RW, Williams RE, Meade TW, Wilkes H, Griffin M. A prospective study of faecal bile acids and colorectal cancer. *Eur J Cancer Prev* 2000; **9**: 317-323 [PMID: 11075884]

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**Table 1 Most common types of drugs used for the treatment of chronic idiopathic constipation and constipation-predominant irritable bowel syndrome**

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| --- | --- | --- | --- | --- | --- | --- | --- |
| **Drug class** | | **Generic name** | **Phase of clinical trial/approval status** | **Proposed mechanism of action** | **Therapeutic effect** | **Most frequent adverse effect** | **Ref.** |
| Secretagogue | Linaclotide | | III/ FDA approval (2012) | GC-C agonist | Antinociceptive and antihyperalgesic. Increases intestinal fluid, accelerates GI transit, reduces abdominal pain. | Mild or moderate diarrhea | [4,8-11] |
|  | Lubiprostone | | III, IV/ FDA approval (2008) | CIC–2 activator | Promotes intestinal fluid secretion, increases SBM frequency, reduces abdominal bloating and discomfort. | Nausea, diarrhea, abdominal distention, headache | [8,12-14] |
|  | Plecanatide | | II, III for CIC and I for IBS–C | GC-C agonist | Facilitates BM, stimulates water secretion, improves stool consistency and frequency. | Diarrhea mild or moderate in severity, nausea, abdominal discomfort, abdominal pain, vomiting (occurred at the highest doses) | [12,15,16] |
| Prokinetic | Tegaserod | | Withdrawn by the FDA in 2007 due to risk of adverse cardiovascular effects | Selective partial 5–HT4 agonist | Stimulates motility in the upper and lower GI tract, reduces visceral sensitivity and pain, improves stool consistency.  Administered twice daily increases gastric emptying rate.  Smooth muscle relaxant, reduces colonic pseudo–obstruction and constipation. | Diarrhea, cardiovascular effect (angina, myocardial infarction and cerebrovascular events) | [12,17-19] |
|  | Renzapride | | II and III for IBS–C/ remains under evaluation | Full 5–HT4 agonist and 5–HT3 receptor antagonist | Prokinetic and stimulatory effect on GI transit, improves stool consistency. | Diarrhea, abdominal pain, constipation, nausea | [8,20-22] |
|  | Prucalopride | | III, undergo clinical trials | 5–HT4 agonist | Improves the frequency of SBM, reduces abdominal discomfort. | Headache, nausea, abdominal pain, diarrhea | [12,14,20] |
|  | Velusetrag  Naronapride | | Completed Phase II | 5–HT4 receptor agonist | Accelerates of colonic and orocecal transit, increases SBM, normalizes of stool consistency | Diarrhea, headache, nausea | [23-25] |
| Laxatives | Lactulose, Sorbitol, Polyethylene glycol  Magnesium citrate | | approved | Osmotic water retention, stimulant | Increases fecal volume and peristalsis | Bloating, cramping and flatulence | [17,26-28] |
| Bile acid modulators | Chenodeoxycholate | | II/ remains under evaluation | Intracellular activation of adenylate cyclase, inhibition of apical Cl-/OH - exchange | Accelerates colonic transit, improves stool consistency | Lower abdominal cramping, diarrhea | [18,27] |

CIC: Chronic idiopathic constipation; BM: Bowel movements; FDA: Food and Drug Administration; GC-C: Guanylate cyclise C; GI: Gastrointestinal tract; IBS–C: Constipation-predominant irritable bowel syndrome; SBM: Spontaneous bowel movement.

**Figure 1 Effect of ileal bile acid transporter in the proximal ileum.** Bile acid synthesis is a major metabolic pathway for catabolism of cholesterol. Primary bile acids (BA), Cholic acid (CA) and chenodeoxycholic acids (CDCA), are obtained *via* the alternative (acidic) pathway, initiated by mitochondrial CYP27A1, or by the classical (neutral) biosynthetic pathway, catalysed by microsomal CYP7A1. CYP7A1 is a rate–limiting enzyme, which regulates the overall rate of BA synthesis in the liver. The activity of CYP7A1 depends upon the quantity of bile acids absorbed in the intestine. Inhibition of ileal bile acid transporter (IBAT) contributes to upregulation of BA synthesis and therefore promotes the maintenance of BA pool size. Simultaneously, a decrease in the concentration of serum LDL and an increase of C4 level, which is a surrogate for CYP7A1 activity, may occur. BACS and BAT are two key enzymes involved in the conjugation of BA to amino acids (G or T). In the intestine, conjugated G/T–CDCA and G/T–CA are dehydroxylated to the secondary bile acids, DCA and LCA. The action of selective IBAT inhibitor increases the concentration of BAs entering the proximal colon, which in turn stimulate colonic motility and secretion resulting in enhanced laxative properties.BACS: Bile acid CoA synthase; BAT: Bile acid amino acid transferase; CYP27A1: Sterol 27 hydroxylase; CYP7B1: Nonspecific 7α–hydroxylase; DCA: Deoxycholic acid; G: Glycine; IBAT: Ileal bile acid transporter; LCA: Lithocholic acid; LDL: Low density lipoprotein; T: Taurine. Based on[34-37] modified.

