New treatment options for chronic constipation: Mechanisms, efficacy and safety

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M Camilleri. New treatment options for chronic constipation: Mechanisms, efficacy and safety. Can J Gastroenterol 2011;(Suppl B):29B-35B.

The present review has several objectives, the first of which is to review the pharmacology and selectivity of serotonergic agents to contrast the older serotonergic agents (which were withdrawn because of cardiac or vascular adverse effects) with the newer generation serotonin receptor subtype 4 agonists. Second, the chloride ion secretagogues that act through the guanylate cyclase C receptor are appraised and their pharmacology is compared with the approved medication, lubiprostone. Third, the efficacy and safety of the application of bile acid modulation to treat constipation are addressed. The long-term studies of surgically induced excess bile acid delivery to the colon are reviewed to ascertain the safety of this therapeutic approach. Finally, the new drugs for opiate-induced constipation are introduced. Assuming these drugs are approved, practitioners will have a choice; however, patient responsiveness will be based on trial and error. Nevertheless, the spectrum of mechanisms and demonstrated efficacy and safety augur well for satisfactory treatment outcomes.

Key Words: *Opiate; Prokinetics; Secretagogues*

De nouvelles options thérapeutiques contre la constipation chronique : leurs mécanismes, leur efficacité et leur innocuité

La présente analyse comporte plusieurs objectifs, le premier étant de réviser la pharmacologie et la sélectivité des sérotoninergiques pour comparer les anciens sérotoninergiques (retirés du marché en raison de leurs effets cardiaques ou vasculaires) avec les agonistes de récepteurs de la sérotonine de sous-type 4 de nouvelle génération. En deuxième lieu, les sécrétagogues des ions chlorures qui agissent par le récepteur du guanylatecyclase C sont évalués, et leur pharmacologie est comparée avec celle du lubiprostone, un médicament approuvé. En troisième lieu, l'efficacité et l'innocuité de l'application de la modulation de l'acide biliaire pour traiter la constipation sont abordées. Les études à long terme sur la livraison excessive d'acide biliaire dans le côlon, induite par la chirurgie, sont analysées afin d'évaluer l'innocuité de cette démarche thérapeutique. Enfin, les nouveaux médicaments contre la constipation induite par les opiacés sont présentés. Si ces médicaments sont approuvés, les praticiens auront un choix, mais la réponse des patients dépendra d'essais-erreurs. Néanmoins, le spectre des mécanismes et l'efficacité et l'innocuité démontrées augurent bien pour l'issue des traitements.

After the exclusion of organic mucosal disease, strictures and evacuation disorders, the treatment of constipation is typically based on single or combined treatments with fibre (1,2), osmotic laxatives (3) and stimulant laxatives (4) – to which many patients respond. The present article addresses newer classes of agents to treat constipation: new-generation serotonergic agents, chloride ion secretagogues acting through the guanylate cyclase C receptor and bile acid modulators. In view of increasingly encountered opiate-induced constipation, the new drugs being tested for this indication are also introduced.

SEROTONIN, RECEPTORS AND OLDER SEROTONERGIC AGENTS

Serotonin (5-hydroxytryptamine [5-HT]) is a ubiquitous molecule in the brain-gut axis, with 95% being present in the enteroendocrine cells of the gastrointestinal (GI) mucosa and, to a lesser extent, in interneurons within the gut plexuses. 5-HT is involved in GI secretion, sensation and motility (5). There are seven 5-HT receptor subtypes (6) and, through the different receptor subtypes, 5-HT induces diverse, sometimes opposite effects depending on the receptors stimulated or the activation of the same class of receptor on different types of enteric neurons activated in different sites in the gut (7), such as contraction in the gastric antrum through cholinergic neurons to accelerate gastric emptying (8) and relaxation in the gastric fundus through nitrergic neurons (9). The roles of 5-HT receptor subtype 3 (5-HT_3) and 5-HT_4 in GI motility have been the most extensively studied; 5-HT_4 receptors are abundantly present in the gut (10). Tegaserod, a 5-HT_4 receptor partial agonist, accelerated small bowel and colonic transit (11) and was efficacious in patients with functional constipation (12) and constipation-predominant irritable bowel syndrome (IBS-C) (13). However, the older generation 5-HT_4 agonists had relatively poor receptor selectivity, which led to rare side effects attributable to effects on other receptors or channels and impacted their risk-benefit profile.

Some 5-HT_4 agonists, such as cisapride, may cause ventricular arrhythmias. Cisapride blocks the hERG K^+ channel (IKr), thereby prolonging the repolarization phase of the ventricular action potential and the QT interval. The relative affinities of cisapride, tegaserod and of the new generation 5-HT_4 agonist, prucalopride, for IKr or for the 5-HT_4 receptor illustrates why cisapride is more likely than tegaserod and prucalopride to cause cardiac arrhythmias (14) (Figures 1 A, B and C).

The tissue concentration of cisapride is increased in overdosing (eg, in pediatric patients), renal failure (lack of excretion), aging (altered pharmacokinetics) or drug interactions that inhibit hepatic CYP 3A4 metabolism, and the therapeutic window between desired GI versus cardiac adverse effects is narrowed further. Cardiac arrhythmia is unrelated to pharmacological activity at the 5-HT_4 receptor itself (15).

The 5-HT receptors 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_4 and 5-HT_7 are located on vascular smooth muscle cells and endothelial cells (16), and are involved in cardiovascular regulation. 5-HT_{1B} agonists induce contraction of arterioles and venules and constrict human coronary arteries (17). 5-HT_{2B} receptors may mediate vasodilation (18), and 5-HT_{1D}, 5-HT_4 and 5-HT_7 receptors induce relaxation of venules.

Tegaserod was withdrawn from the market after an analysis found that 13 of 11,614 treated patients experienced ischemic cardiovascular events compared with one of 7031 patients given placebo (19). It is currently believed that lack of selectivity of tegaserod for 5-HT_4 receptors (20) and its affinity for 5-HT_{1B} and 5-HT_{2A} receptors may have resulted in the cardiovascular risk.

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Received for publication April 8, 2011, Accepted June 10, 2011

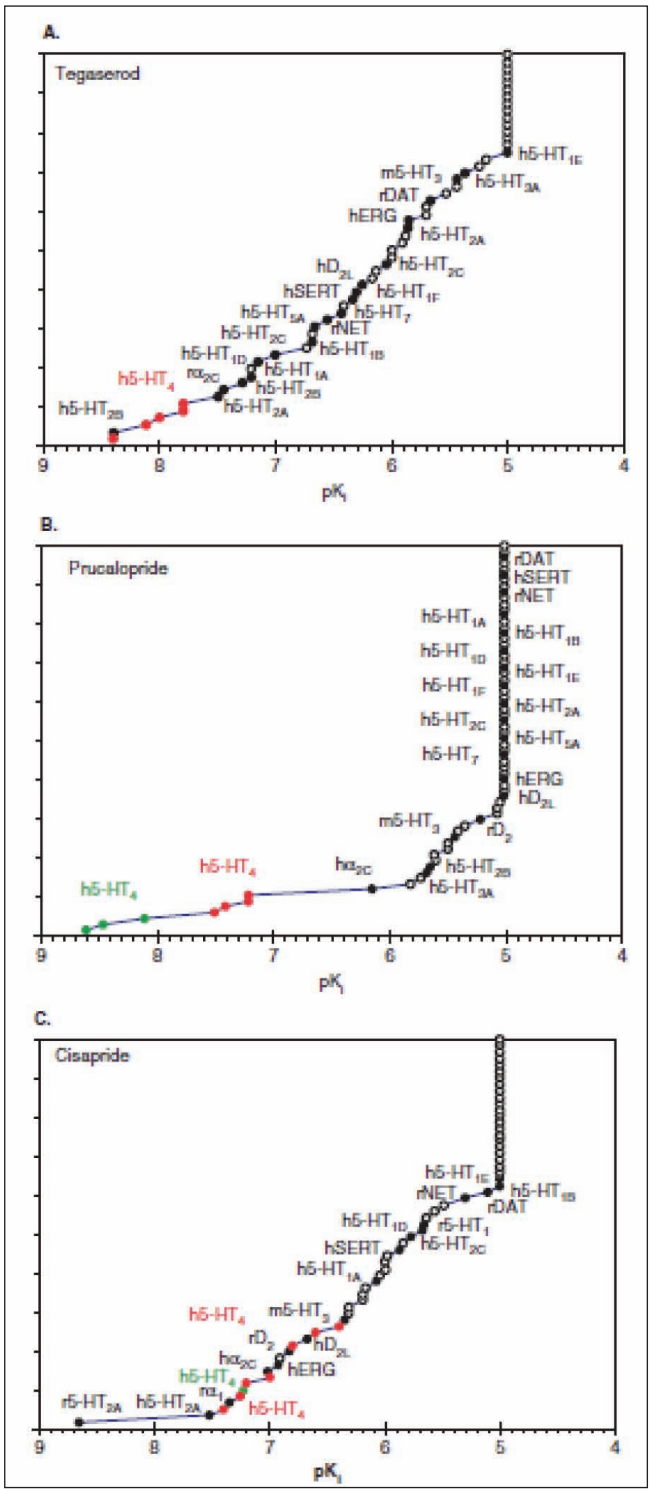

Figure 1) *Selectivity of the human serotonin (h5-HT) receptor subtype 4 (5-HT$_4$) agonists tegaserod (**A**), prucalopride (**B**) and cisapride (**C**). Note the lack of selectivity for the hERG channel of cisapride relative to tegaserod and prucalopride. h Human; D dopamine; rDAT Rat dopamine transporter; hERG Human ether-a-go-go related gene; hNET Human norepinephrine transporter; hSERT Human serotonin transporter. Reproduced with permission from reference 14*

NEW TREATMENT OPTIONS FOR CONSTIPATION NOT ASSOCIATED WITH EVACUATION DISORDERS

Inexpensive treatments, such as fibre, osmotic and stimulant laxatives, that are available over the counter in many countries should be tried first – after exclusion of an evacuation disorder – in primary care settings and in gastroenterology clinics. Voderholzer et al (1) showed that patients who do not respond to these therapies may have constipation due to an evacuation disorder, slow-transit constipation or medication. Lubiprostone is an intestinal secretagogue that has been approved for chronic constipation (CC) and constipation-predominant IBS (IBS-C).

There are three general categories of medications that are being developed for the treatment of chronic idiopathic constipation: colonic prokinetics in the 5-HT$_4$ agonist class, intestinal secretagogues and bile acid modulators. In addition, there are more specific medications being developed for opioid-induced constipation (OIC).

5-HT$_4$ agonists

The 5-HT$_3$ and 5-HT$_4$ receptors have been the most extensively studied targets of prokinetics in humans. They induce fast excitatory postsynaptic potentials in intrinsic neurons, release neurotransmitters such as acetylcholine, and induce mucosal secretion by activating submucosal neurons. Table 1 summarizes the three main candidate 5-HT$_4$ agonists in development: prucalopride, velusetrag and naronapride (21). Their specificity and cardiovascular safety differ from those of the older 5-HT$_4$ agonists (14,22).

The newer 5-HT$_4$ agonists exhibit high intrinsic activity and selectivity at intestinal 5-HT$_4$ receptors, and facilitate cholinergically mediated contractions; however, they have low intrinsic activity in other tissues, including cardiac muscle, thus achieving the desirable selectivity of action and probable cardiovascular safety.

There is considerable evidence supporting prucalopride's pharmacodynamic (23,24) and clinical trial efficacy in patients with CC (25-27), and it is safe in elderly patients (28). Doses of 2 mg per day in adults and 1 mg per day in elderly patients were approved for CC by the European Agency for Evaluation of Medicinal Products.

In vitro, velusetrag is a specific 5-HT$_4$ agonist (29) and has been shown to be safe and efficacious in vivo in animals (30), in pharmacodynamic studies in humans (31) and in a large (400 patient) phase-IIB study (32). Velusetrag has one metabolite that is almost as potent as the parent drug.

Naronapride also shows pharmacodynamic efficacy in animals and humans (33,34). Although chemically related to cisapride, it does not undergo CYP3A4 metabolism and should, therefore, avoid the drug interactions that contributed to arrhythmias with cisapride.

Intestinal chloride secretagogues

These secretagogues increase intestinal chloride secretion with associated secretion of water into the lumen. There are several different classes of chloride channels (ClC), including ClC-2 and ClC-3, which are expressed in most cells. The chloride ions that are secreted from enterocytes or colonocytes enter the cell through the basolateral Na^+-K^+-$2Cl^-$ cotransporter. The cations Na^+ and K^+ are then exported through the Na^+ pump (ie, Na^+/K^+-ATPase) and KCNQ1/KCNE3 heteromeric K^+ channels. Chloride secretory pathways in the apical membrane of epithelial cells include the cystic fibrosis transmembrane regulator (CFTR) and ClC-2 chloride channels (35).

Lubiprostone is a bicyclic fatty acid derived from prostaglandin E1. It activates apical membrane CIC-2 channels (36) and CFTR (37) to stimulate intestinal and colonic secretion of chloride-rich fluid into the intestinal lumen. Lubiprostone may also activate prostaglandin EP receptors (38).

Lubiprostone accelerated intestinal and colonic transit in healthy subjects (39) without significantly impacting colonic motility or sensation as measured by intraluminal probes in humans (40). Lubiprostone does not stimulate uterine smooth muscle in vitro (41), and it inhibits neuronally mediated contractions of colon circular muscle (38). Clinical trials have demonstrated that lubiprostone is efficacious and safe in patients with CC, and is marketed at a dose of 24 µg twice daily for this indication (42,43). Lubiprostone is reported to cause nausea in approximately 20% of patients.

Linaclotide and plecanatide activate secretion of chloride through guanylcyclase C (GC-C). GC-C is enriched in intestinal epithelium,

TABLE 1
Comparison of novel serotonin (5-HT) receptor subtype 4 (5-HT$_4$) agonists

Characteristic	Prucalopride	Velusetrag	Naronapride
Chemistry	Benzofuran carboxamide	Quinolinone-carboxamide	Benzamide
Selectivity and affinity for 5-HT$_4$ receptor	Highly selective, high affinity; weak affinity for human D4 and σ1, and mouse 5-HT$_3$ receptors at concentrations exceeding the K_i for 5-HT$_4$ receptors by 290-fold	High affinity and selectivity for h5-HT$_{4c}$ over other biogenic amine receptors; >500-fold selective over other 5-HT receptors (including h5-HT$_{2B}$, h5-HT$_{3A}$)	Specific 5-HT4 full agonist activity in the GI tract, but a partial agonist activity in the heart
Metabolism	Limited hepatic, not CYP 3A4	CYP 3A4	Hydrolytic esterase, not CYP 3A4
Pharmacodynamic efficacy in humans	Accelerated colonic transit in health and chronic constipation	Accelerated colonic transit in health in dose-related fashion	Accelerated colonic transit in health
Clinical trial efficacy	Phase II and III portfolio in chronic constipation	Phase IIB	Phase IB
Open-label effectiveness	Open-label experience of ~1000 cumulative patient-years	–	–
Arrhythmogenicity	No arrhythmic activity in human atrial cells; inhibited hERG channel only at μM concentration (IC_{50} ~4.9×10^{-6} M); no clinically relevant cardiac adverse events in clinical trials of >4000 human subjects	At 3 μM, no effect on hERG channel current; safety ratio versus cisapride >1000-fold; no effect on QT in health or 400 patients with constipation	At 100 μM, no effect on hERG channel; affinity ratio between I_{Kr} and 5-HT$_4$ receptors of >1000 fold
Cardiovascular safety including elderly	Healthy subjects "thorough" QTc study; safety in elderly cohort 80% on cardiovascular drugs	Healthy subjects "thorough" QTc study; transient increase in heart rate not different from placebo	Healthy subjects "thorough" QTc study
Most common adverse events	Diarrhea, headache	Diarrhea, nausea, headache	Diarrhea, headache
Approval status	EMEA	–	–

Data from reference 21. EMEA European Agency for Evaluation of Medicinal Products; GI Gastrointestinal; h Human; hERG Human ether-a-go-go related gene; IC Inhibitory concentration; I_{Kr} delayed rectifier K^+ channel; QTc Corrected QT interval

TABLE 2
Comparison of the secretagogues lubiprostone and linaclotide

Characteristic	Lubiprostone	Linaclotide
Chemistry	Bicyclic fatty acid called a prostone	14 amino acid peptide, analogue of guanylin
Target receptor	Chloride channel (ClC2); ? CFTR involved	Guanylate cyclase C receptor activation with CFTR-mediated secretion
Pharmacodynamics in humans	Accelerated small bowel and colonic transit in health	Accelerated colonic transit in constipation-predominant irritable bowel syndrome in dose-related fashion
Clinical trial efficacy	Phase II and III portfolio in chronic constipation and constipation-predominant irritable bowel syndrome	Phase IIB in chronic constipation and constipation-predominant irritable bowel syndrome
Open-label effectiveness	Clinical practice experience	–
Arrhythmogenicity	No arrhythmic activity	Low bioavailability no arrhythmic activity
Cardiovascular safety	Healthy subjects "thorough" QTc study	Healthy subjects "thorough" QTc study
Most common adverse events	Diarrhea, nausea	Diarrhea
Potential other actions	Mucosal protection	Antineoplastic
Approval status	United States Food and Drug Administration	–

Data from reference 21. CFTR Cystic fibrosis transmembrane conductance regulator; QTc Corrected QT interval

although it is detected in other epithelia. It is the receptor responsible for heat-stable enterotoxin (STa) *Escherichia coli* diarrhea; these enteric bacterial peptides are 19 amino acids (AAs) in length (44). There are two endogenous ligands of GC-C: the small cysteine-rich peptides, guanylin (15 AA) and uroguanylin (16 AA). These peptides are released in an autocrine or paracrine fashion into the intestinal lumen; they also function as endocrine hormones regulating ion transport in extraintestinal epithelia (eg, kidney).

In the intestine, activation of GC-C results in the stimulation of chloride and bicarbonate secretion through the opening of apical CFTR chloride channels and inhibition of sodium absorption through blockade of an apical Na^+/H^+ exchanger. The principal effector of the GC-C effect on ion transport is cyclic GMP-dependent protein kinase type II.

Linaclotide is a 14 AA peptide that contains three disulfide bonds required for GC-C activation. The active metabolite, MM-419447, is produced after loss of the C-terminal tyrosine through the action of carboxypeptidase A. By increasing cyclic GMP levels, linaclotide stimulates chloride and bicarbonate secretion through CFTR channel-dependent and, to a lesser extent, channel-independent mechanisms (45). Linaclotide also inhibits sodium absorption from the lumen via a sodium proton exchanger (46). Linaclotide accelerated colonic transit (47), enhanced intestinal secretion (48) and improved symptoms in patients with CC (49,50).

Plecanatide (SP-304) is a synthetic analogue of uroguanylin in development for IBS-C and CC. It was tested in early studies (51) to characterize its safety and pharmacokinetics, and to obtain early efficacy demonstrated by altered stool consistency. In addition, it improved symptoms of constipation such as frequency, consistency, straining and abdominal discomfort in 80 patients with CC in the first phase-IIA 14-day treatment study of daily doses of 0.3 mg, 1 mg, 3 mg and 9 mg (52).

Table 2 summarizes the properties of lubiprostone and linaclotide (21).

Bile acid modulation

Under physiological conditions, approximately 95% of bile acids secreted into the duodenum are actively reabsorbed in the terminal ileum. Inadequate reabsorption and delivery of bile acids into the colon result in secretory diarrhea (53), chiefly by increasing permeability (54) or by activating adenylate cyclase (55). Both conjugated and nonconjugated bile acids induce secretion in the human colon

TABLE 3
Pharmacological approaches to treat opiate-induced constipation (OIC)

Drug name	Drug class	Pharmacodynamic efficacy in humans	Clinical trial optimal efficacy and safety	Ref(s)
Naloxone	Nonselective opioid antagonist	Reverses opiate-induced delay in orocecal and colonic transit	Naloxone PR formulation prevents OIC in patients receiving PR oxycodone	72–77
Methyl naltrexone (MNTX)	M-opioid antagonist	Reverses effects of opiate in health and of chronic methadone treatment on orocecal transit; no effect on small intestinal or colonic transit delayed by codeine 30 mg qid in opiate-naive healthy subjects	Subcutaneous MNTX 0.15 mg/kg on alternate days effective in inducing laxation in patients with advanced illness	78–85
Naltrexone ER	M-opioid antagonist as sequestered core: ratio naltrexone to morphine 4%	ND	Open-label 12-month safety of combination extended-release pellets of morphine (median 59 mg/day) with a sequestered naltrexone core (qd or bid): OIC 31.8%, nausea 25.2%; opiate withdrawal <5%	86
Alvimopan	PAMORA	8 mg oral dose accelerates colonic transit and reverse effects of codeine in opiate-naive healthy volunteers receiving codeine 30 mg qid	0.5 mg bid dose efficacious in treating OIC; rare instances of ischemic heart disease	87,88
NKTR-118	PAMORA; PEGylated naloxol conjugate	Normalized morphine-induced delay in orocecal transit	25 mg and 50 mg NKTR-118 had increased number of SBM during the first week and overall 4 weeks of treatment of OIC patients	89,90
TD-1211	PAMORA	ND	5 mg/day and 10 mg/day TD-1211 increased average SBM/week over 2 weeks in OIC patients	91
Tapentadol	M-opioid agonist plus norepinephrine reuptake inhibitor	ND	Tapentadol ER 100–250 mg bid equally effective for moderate to severe chronic osteoarthritis-related knee pain or chronic low back pain compared with oxycodone HCl (CR) 20 mg to 50 mg bid daily with less bowel dysfunction symptoms	92–94

bid Twice per day; CR Controlled release; ER Extended release; ND Not done; PAMORA Peripherally restricted μ (M)-opioid receptor antagonist; PEG Polyethylene glycol; PR Prolonged release; qd Once per day; qid Four times per day; SBM Spontaneous bowel movements. Data from reference (Ref) 71

(56,57); hence, the delivery of any excess bile acids to the colon can result in secretion. Bile acids also increase colonic motility (58,59), although the most effective dose is unclear. Ileocolonic delivery of sodium chenodeoxycholate (CDC) results in accelerated colonic transit, increased stool frequency and consistency in healthy volunteers, and in patients with IBS-C (60,61) at relatively low doses of 0.5 g/day to 1.0 g/day, whereas higher doses (2.25 g/day) of oral CDC were of variable efficacy in patients with CC (62).

A novel approach to deliver bile acids to the colon to treat CC involves the inhibition of the ileal bile acid transporter (IBAT, also known as the apical sodium-dependent bile acid transporter). A3309 is a selective inhibitor of the IBAT and has been shown to reduce meat-induced constipation in dogs (63). In humans, A3309 enhanced colonic transit in a multiple ascending dose, phase-IB study in patients with chronic idiopathic constipation (64). In a single-centre, pharmacodynamic, placebo-controlled study of 15 mg and 20 mg doses of A3309, Wong et al (65) demonstrated that A3309 accelerated colonic transit at 24 h and 48 h, and had significant effects on stool consistency, constipation rating, ease of stool passage and reduction of straining. Treatment was associated with increased serum levels of 7α-hydroxy-4-cholesten-3-one, consistent with stimulation of hepatocyte bile acid synthesis as a result of inhibition of ileal bile acid absorption.

In a randomized, placebo-controlled, eight-week, multicentre, parallel-group, phase-IIB trial of 190 patients, Chey et al (66) evaluated the effects of a one-week treatment with 5 mg, 10 mg and 15 mg of A3309 (66), and observed that the 10 mg and 15 mg doses significantly increased stool frequency and improved constipation-related symptoms during the first week. The beneficial effects were maintained over the eight-week treatment period.

Malabsorbed bile acids have the potential to induce neoplastic transformation in the colonic epithelium if the latter is also exposed to a carcinogen in an experimental model (67). The data from long-term follow-up studies of patients after partial ileal bypass performed for hyperlipidemia (68) are reassuring. There was no increased prevalence of colorectal cancer at five years follow-up (1.9% colorectal cancers in the control group and 2.4% in the surgery group; P=0.69). A 25-year, long-term follow-up study did not reveal any differences in cancer rate (11% in the control group and 9% in the surgery group [69]). In a recent review, Bajor et al (70) concluded that there is no firm evidence that clinically relevant concentrations of bile acids induce colon cancer.

NEW APPROACHES TO TREAT OIC

OIC is experienced by approximately 40% of patients who receive chronic treatment with opioids for chronic noncancer pain. The experience of constipation and other GI symptoms may dissuade patients from using the required analgesic dose to achieve effective pain relief. Opiates have several effects on GI function, and the inhibition of colonic transit and intestinal and colonic secretion result in constipation. Several different pharmacological approaches are being developed to prevent or treat OIC: prolonged-release formulations that contain naloxone (a less-specific opiate antagonist that is widely distributed); and a new class of peripherally-restricted μ-opiate receptor antagonists including methyl naltrexone, alvimopan, tapentadol, NKTR-118 and TD-1211. These agents are summarized in Table 3 (71).

Because OIC is not the main focus of the current article, the individual trials are not discussed; they are, however, referenced in Table 3 (72-94). In addition, lubiprostone and prucalopride have been reported to relieve OIC (95,96).

CONCLUSION

The novel therapeutic options for CC appear to be safe and efficacious, and activate diverse mechanisms to induce increased motility or secretion in both the small bowel and colon (eg, lubiprostone, linaclotide and plecanatide) or predominantly in the colon (eg, A3309). Current studies do not differentiate patients with abnormal secretion as the cause of constipation, normal or delayed colonic transit constipation. Thus, after these drugs are approved, practitioners will have a choice; however, patient responsiveness will be based on trial and error. Nevertheless, the spectrum of mechanisms, and demonstrated efficacy and safety augur well for satisfactory treatment outcomes.

ACKNOWLEDGEMENTS: The author gratefully acknowledges the excellent secretarial support of Mrs Cindy Stanislav.

DISCLOSURES: Dr Camilleri has received research grants from Theravance, ARYx, Takeda-Sucampo, Microbia, Albireo, Adolor, and Wyeth to study pharmacodynamic effects of velusetrag, naronapride, lubiprostone, linaclotide, A3309, alvimopan, and methylnaltrexone, respectively. He also served on advisory boards for these companies and Synergy (regarding plecanatide) when he was not conducting research on the drugs. He received personal compensation that was below the federal threshold for significant conflict of interest for serving as an advisor.

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