Chronic constipation: new diagnostic and treatment approaches

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Abstract: Chronic constipation is a highly prevalent disorder that affects approximately 15% of the US population. Chronic constipation refers to patients who have had symptoms for more than 6 months. In clinical practice, chronic constipation is often used interchangeably with the term functional constipation. This is best defined using the Rome III criteria, which involves an evaluation of stool frequency in addition to symptoms of straining, feelings of incomplete evacuation, and the need to use manual maneuvers to assist with stool evacuation. Symptoms can be burdensome, leading to a reduction in patients' quality of life. As a national healthcare issue, chronic constipation is also important because it imposes a significant economic impact on the healthcare system. A number of treatment options are currently available, both over-the-counter and by prescription, although not all patients respond to these therapies. This review will focus on new medical treatment options for the management of chronic constipation, and the safety and efficacy of these agents will be reviewed. In addition, the efficacy of new diagnostic tests to evaluate colonic motility and anorectal function are described.

Keywords: anorectal manometry, constipation, guanylate cyclase, linaclotide, lubiprostone, plecanitide, prucalopride, Rome criteria, velusetrag, wireless motility capsule

Introduction

Chronic constipation (CC) is a highly prevalent, heterogeneous disorder that significantly affects patients' lives. Estimates on the prevalence of constipation vary based on how the disorder is defined; a recent review estimated the overall prevalence of constipation in the US to be approximately 15% [Higgins and Johanson, 2004]. Recent studies have demonstrated that CC reduces patients' quality of life and imposes a significant economic burden to the healthcare system [Irvine *et al.* 2002; Sonnenberg and Chang, 2008]. Clinical research using validated questionnaires (e.g. SF-36 and PAC-SYM) have demonstrated that older adults (> 65 years) with constipation have a marked reduction in quality of life [Frank *et al.* 1999; O'Keefe *et al.* 1992; Whitehead *et al.* 1989]. Other studies, which included adults of all ages, found similar results. For example, a multinational prospective survey (using the SF-36) of 1435 adults with constipation (Rome III criteria) found that quality of life was markedly reduced compared with nonconstipated controls [Wald *et al.* 2007]. Analysis of the

National Health and Wellness Survey (NHWS), which used the SF-12 questionnaire, found that patients with constipation ($n = 1430$) had lower physical and mental component scores compared with matched controls ($n = 1430$) without constipation [Sun *et al.* 2011].

The significant economic costs associated with treating CC arise due to direct costs associated with evaluation and treatment, as well as indirect costs, such as missing school or work (absenteeism) or not being as productive at school or work as usual (presenteeism). In the adult population the primary symptom of constipation led to 6.3 million patient visits in the US in 2004 [Everhart and Ruhl, 2009; Martin *et al.* 2006]. Another analysis, using data from the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS), found that ambulatory care visits for constipation in the US increased from 4 million during 1993–1996 to 8 million during 2001–2004 [Shah *et al.* 2008]. A large survey study from a health maintenance organization (HMO; with

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Table 1. Rome III definition of functional constipation (modified from Longstreth, 2006).

- Symptom onset at least 6 months prior to diagnosis
- Presence of symptoms for the last 3 months (see below)
- Insufficient criteria for irritable bowel syndrome
- Loose stools are rarely present without the use of laxatives
- Less than three bowel movements per week
- Symptoms include two or more of the following during at least 25% of defecations:
 - Straining
 - Lumpy or hard stools
 - Sensation of incomplete evacuation
 - Sensation of anorectal obstruction or blockade
 - Manual maneuvers to facilitate evacuation

>525,000 members) found that annual health-care costs for patients with CC were US\$7522, nearly 50% higher than for patients with irritable bowel syndrome (IBS; US\$5049) [Nyrop *et al.* 2007]. The long-term costs of CC were highlighted in a study by Choung and colleagues who found that direct medical costs were double those of controls over a 15-year period (US\$63,591 *versus* \$24,529) [Choung *et al.* 2011]. The authors noted that women with a diagnosis of constipation used more of all types of services, ranging from outpatient clinics to emergency department visits.

Chronic constipation defined

Data from clinical trials and basic science research performed during the past decade has greatly improved our understanding of the etiology and pathophysiology of CC. In light of these findings, the definition of constipation has also changed. The Rome II criteria defined functional constipation as the presence of 2 or more symptoms of constipation present for at least 12 weeks out of the prior 12 months (see Table 1) [Thompson *et al.* 1999]. The Rome III criteria (see Table 1) now defines functional constipation over a shorter period of time (active symptoms within the last 3 months and symptom onset at least 6 months previously), in addition to using a number of different symptoms, including stool frequency, straining at stool, feelings of incomplete evacuation, the need for digital manipulation, and rectal

pressure or pain [Longstreth, 2006]. The Rome III criteria, in contrast to the Rome II criteria, also clarified the point that loose stools should rarely be present without the use of laxatives.

In clinical practice, functional constipation is frequently referred to as CC, a well-recognized term that acknowledges the chronicity of symptoms, incorporates the criteria for functional constipation, and excludes IBS. The broader definition of functional constipation noted in the latest iteration of the Rome criteria is valuable in clinical practice because it should improve communication between patients and physicians, since patients and physicians frequently differ dramatically in their definition of constipation [Lembo and Camilleri, 2003]. For example, one study showed that a patient's definition of constipation agreed with a physician's definition only 50% of the time and most often focused on symptoms rather than stool frequency [Herz *et al.* 1996]. In addition, the current Rome III criteria properly include patients with symptoms of constipation (e.g. straining, incomplete evacuation, and need for manual maneuvers) who were improperly excluded before based on normal stool frequency. In fact, patients use stool frequency as a measure of constipation only 32% of the time [Sandler and Drossman, 1987]. Patients are more likely to report that they are constipated if they have straining at stool (52%), have hard stools (44%), have the urge to pass stool but cannot (34%), or have abdominal discomfort (20%). Analysis of the National Health Interview Survey data from 1999 found that, in 10,875 subjects older than age 60, straining and hard bowel movements were most strongly associated with self-reported constipation [Harari *et al.* 1997].

The Rome III classification included new diagnostic criteria for several functional bowel disorders, in addition to IBS. When one considers the broad umbrella term of 'constipation', both IBS with constipation and functional constipation are included. In order to keep this update focused; this review will focus on functional (chronic) constipation. One important point about the Rome III criteria for functional constipation is that there are insufficient criteria for IBS. In clinical practice that means that lower abdominal pain or discomfort should not be present to any significant degree.

New diagnostic tests

Routine diagnostic testing is not recommended in all constipated patients in the absence of warning signs (e.g. hematochezia, anemia, family history of colorectal cancer, and unintentional weight loss). In general, the yield of diagnostic testing is low and treatment should be individualized with an emphasis on symptom improvement. Patients who continue to have persistent symptoms despite medical therapy are frequently referred for colonoscopy to exclude mechanical obstruction, although this test does not provide any meaningful data on colorectal function. Anorectal manometry with a balloon expulsion test can help identify patients with an evacuation disorder due to pelvic floor dysfunction, while a Sitz mark study can be used to assess colonic transit [Lembo and Camilleri, 2003]. The Sitz mark study is not required for all patients with symptoms of constipation, however, and is best suited for those patients thought to have slow transit constipation (colonic inertia).

In some patients with persistent symptoms of constipation, a Sitz mark test may be difficult to perform, however, due to a lack of ready access to a radiology suite, while in other patients with overlapping symptoms suggestive of an upper gastrointestinal (GI) tract motility disorder, more comprehensive testing may prove useful. As well, there is a lack of standardization regarding the performance of a Sitz mark study, and there are appropriate concerns about radiation exposure. For these reasons, a new diagnostic test was developed, called the wireless motility capsule. The wireless motility capsule, given the name SmartPill by the manufacturers (SmartPill Corporation, Buffalo, NY), is similar in size to a video capsule (27 mm × 12 mm). This single-use capsule contains sensors to measure temperature (range of 25–49°C), pH (range of 0.05–9.0 pH units), and pressure (range of 0–350 mmHg). The study begins by having the patient ingest a standard meal (a 260 kcal nutrient ‘SmartBar’) along with 50 ml of water. The capsule is then activated and the patient swallows the capsule. For the next 3–5 days the patients wears a receiver and performs his/her usual activities. After the capsule has passed through the GI tract the data is downloaded to a computer for analysis. Transit time throughout the entire GI tract can be measured (also called the whole gut transit time). In addition, using changes in pH values and changes in

pressure recordings, the wireless motility capsule can be used to measure individual components of whole gut transit, including gastric emptying, small bowel transit, and colonic transit. The wireless motility capsule (SmartPill) was approved by the FDA in July 2006. It is not approved for use in the pediatric population. Contraindications to use include: dysphagia; known strictures, fistulas, or mechanical obstruction of the GI tract; surgery to the GI tract within the past 3 months; Crohn’s disease; diverticulitis; and the presence of cardiac defibrillators and infusion pumps.

Several peer-reviewed manuscripts have been published on the use of the wireless motility capsule. Three are worth mentioning. The first study was a multicenter study comparing the wireless motility capsule to radiopaque markers (ROMs) in the evaluation of regional and colonic transit time (CTT) in healthy volunteers ($n = 87$) and patients with constipation (Rome II criteria; $n = 78$). After an overnight fast, patients ingested a standard nutrient bar, followed by a single Sitzmark capsule (containing 24 markers) followed by a wireless motility capsule. They returned 48 (day 2) and 120 hours (day 5) later for an abdominal X-ray. Rao and colleagues found that the correlation coefficient between CTT using the wireless motility capsule and the ROM test on day 5 was $r = 0.59$ for the entire group [Rao *et al.* 2009]. It was somewhat better in constipated subjects ($r = 0.69$) and worse in healthy volunteers ($r = 0.40$). The sensitivity and specificity for identifying abnormal colonic transit in patients with constipation was 0.46 and 0.95, respectively. No adverse events (AEs) occurred in any patient ingesting the capsule.

A second prospective, multicenter trial compared colonic transit measurements using ROMs to the wireless motility capsule [Camilleri *et al.* 2010]. This study involved 158 patients (87% women; mean age = 43 years) with symptomatic constipation, and was designed to demonstrate equivalence between the two different tests, defined in advanced as diagnostic agreement for >65% of the patients. The authors reported that the percentage positive agreement between the two studies (both with evidence of delayed transit) was 80%. The percentage negative agreement between the two studies (both studies showed no evidence of impaired colonic transit) was 91%. Overall, this study shows that the wireless

motility capsule provides a reasonable estimate of colonic transit and has good agreement with ROM studies, which many consider the standard of care for measuring colonic transit.

The last study that warrants a brief mention is a retrospective review of 83 patients studied with the wireless motility capsule at 2 different centers [Kuo *et al.* 2011]. The results of the wireless motility capsule were reviewed in the context of previously reported symptoms, recorded prior diagnoses, and prior tests and treatments. Kuo and colleagues noted that wireless capsule testing provided a new diagnosis in 53% of patients and influenced management in 67% of patients. Although limited by the sample size and the retrospective nature of the study, this report is interesting because it attempts to measure the clinical utility of a new technology. A large, prospective study is obviously required to verify these results.

In summary, these studies demonstrate that the wireless motility capsule can fairly reliably measure colonic transit and whole gut transit. It appears to be as good as the radiopaque marker study, although it is more expensive and requires specialized technology that is available currently at only a small number of medical centers. The clinical utility of wireless capsule testing in patients with the diagnosis of functional constipation will need to be determined in a large, prospective, multicenter study. Future research is needed to compare the utility of the wireless motility capsule with both antroduodenal manometry and colonic manometry, for the evaluation of upper small intestine and colonic motility, respectively.

High-resolution anorectal manometry

High-resolution manometry (HRM) is a new diagnostic technique used to evaluate anorectal function and physiology. HRM has primarily been used in the esophagus, where it has been shown to provide both new information and a greater breadth of information than standard solid state manometry. HRM has not been well studied in the anorectum. Although HRM catheters may vary from company to company, the catheters are all fairly similar in that they have multiple radial sensors (12–36 on average, spaced 1 cm apart) combined with a rectal balloon. Multiple sensors are positioned across the anal canal, while others are positioned with the rectal

balloon. Standard measurements can be taken at rest, during voluntary contraction, during straining, and during rectal balloon distensions. One study compared simultaneous standard water perfused anorectal manometry to anorectal HRM [Jones *et al.* 2007]. In this study of 29 patients referred for anorectal manometry, anorectal HRM provided greater resolution of intraluminal pressures compared with standard manometry. Future studies are needed to determine whether anorectal HRM should become the standard of care in all motility laboratories.

Current treatment options

The treatment of CC can be frustrating for both patients and healthcare providers because symptoms do not always accurately reflect the underlying pathophysiology nor do they predict response to treatment. Many patients initiate treatment on their own by drinking more water, exercising, and adding dietary fiber. These lifestyle modifications are safe, although usually ineffective except in patients who are fiber deficient [Muller-Lissner *et al.* 2005; Young *et al.* 1998]. Patients with persistent symptoms then generally use over-the-counter medications, which include bulk laxatives (e.g. psyllium), osmotic laxatives (e.g. magnesium citrate), emollients (e.g. docusate sodium), and stimulant laxatives (e.g. cascara). Although some patients note an improvement in symptoms, there is little evidence documenting long-term clinical efficacy of these agents [Brandt *et al.* 2005]. Persistent symptoms of constipation then prompt many patients to seek consultation with their healthcare provider. After an appropriate evaluation has been performed, medical therapy is usually recommended, and this may include osmotic agents (e.g. lactulose, polyethylene glycol) or a chloride channel activator (e.g. lubiprostone; see Figure 1). The safety and efficacy of these agents has been the subject of several comprehensive reviews [Cash and Lacy, 2006; Crowell *et al.* 2009; Lacy and Chey, 2009]. Newer and upcoming agents to treat constipation are discussed in the following.

Prucalopride

Prucalopride is an orally-administered dihydrobenzofurancarboxamide derivative shown to be a potent, selective, high-affinity agonist at the 5-HT₄ receptor (see Figure 2). The pharmacokinetic parameters were evaluated in 12 adults after repeated oral dosing of 2 mg prucalopride

Figure 1. Structure of lubiprostone.

Figure 2. Structure of prucalopride.

succinate [Janssen Research Foundation, 1999]. The plasma elimination half-life was about 24 hours with maximum concentration observed approximately 3 hours after a dose. The drug appears to be well absorbed with oral bioavailability estimated at 90%. Most of the drug is eliminated in the urine (60–70%) and the pharmacokinetic profile is not altered by the administration of food [Van de Velde *et al* 2009].

The safety and efficacy of prucalopride has been evaluated in three large studies [Camilleri *et al.* 2008; Quigley *et al.* 2009; Tack *et al.* 2009]. All three studies were 12 weeks in duration and were similar in design: multicenter, randomized, double-blind, placebo-controlled, and parallel group.

Patients were defined as having CC if they had two or fewer complete spontaneous bowel movements (CSBMs) each week for a minimum of 6 months before the screening visit. Patients also had to have very hard or hard stools, or straining with at least 25% of bowel movements. Symptoms were measured during a 2-week observation period and then patients were randomized to once-daily prucalopride (2 or 4 mg) or placebo. The primary efficacy endpoint was the proportion of patients having three or more CSBMs per week, averaged over the 12-week period, using an intention-to-treat analysis. The main secondary endpoint was the percentage of study patients with an average increase of one or more CSBMs per week. Other secondary endpoints included the median time to the first CSBM, changes in stool consistency and straining at stool, and satisfaction with bowel habits. In the study by Camilleri and colleagues [Camilleri *et al.* 2008], 628 patients were randomized to study drug and 620 patients (88% women; mean age = 48 years) were included in the study analysis. The primary endpoint (3 or more CSBMs/week) was reached by 31% of those on 2 mg of prucalopride, 28% of those on 4 mg, and 12% of those on placebo ($p < 0.001$ for both study groups; see Table 2). During the 12-week study period, more patients treated with prucalopride had an increase of one or more CSBM/week when treated with either 2 mg (47%) or 4 mg of prucalopride (47%) compared with placebo (26%; $p < 0.001$ for both doses). More patients rated their treatment as effective or extremely effective at week 12 when treated with prucalopride (33–37%) compared with placebo (17%; $p < 0.001$). AEs are described below.

Tack and colleagues randomized 720 patients with CC to prucalopride (2 or 4 mg) or placebo in a multicenter trial conducted in 7 countries [Tack *et al.* 2009]. The mean duration of constipation was approximately 18 years and the

Table 2. Summary of prucalopride phase III clinical trials.

	Dose	Camilleri <i>et al.</i> [2008]	Tack <i>et al.</i> [2012]	Quigley <i>et al.</i> [2012]
Percentage of women		88%	90.8%	86.6%
Mean age (years)		48.3	43.9	47.9
Mean duration of symptoms (years)		21.1	17.5	22.0
Total randomized		628	720	651
Total completed		534 (85%)	597 (83%)	567 (89%)
Total evaluated		620	713	641
	Placebo	209	240	212
	2 mg	207	236	214
	4 mg	204	237	215
Mean CSBMs/week (at baseline)		0.4–0.5	0.4–0.5	0.4–0.5
≥3 CSBMs/week	Placebo	12%	9.6%	12.1%
	2 mg	30.9%^	19.5%#	23.9%#
	4 mg	28.4%^	23.6%^	23.5%#
Increase in ≥1 CSBMs/week	Placebo	25.8%	20.9%	27.5%
	2 mg	47.3%^	38.1%^	42.6%^
	4 mg	46.6%^	44.1%^	46.6%^
Median time to 1st CSBM (in days)	Placebo	12.6	20.5	13.0
	2 mg	1.3^	4.7^	2.3
	4 mg	1.0^	2.1^	1.9

Note: * $p < 0.05$; # $p < 0.01$; ^ $p < 0.001$
CSBM, complete spontaneous bowel movement

average number of CSBMs in each group was 0.4–0.5 per week. During the 12-week study period, prucalopride (both 2 and 4 mg daily) resulted in a larger number of patients meeting the primary end point, compared with placebo (see Table 2). Patients treated with prucalopride were more likely to rate their treatment as quite effective or extremely effective (35–36%), compared with placebo (19%; $p < 0.001$). Patients treated with prucalopride also reported an improvement in several secondary endpoints, compared with placebo, including: the percentage of patients with an increase of 1 or more spontaneous bowel movements (SBM) per week ($p < 0.001$); the percentage of bowel movements with normal consistency ($p < 0.05$ for both groups); and the percentage of bowel movements not associated with straining ($p < 0.01$ for both groups). AEs are described below.

The third study was a multicenter trial involving 41 sites in the United States and using the protocol described above; this study also showed a statistically

significant improvement in the primary endpoint over the 12-week period for patients treated with prucalopride [Quigley *et al.* 2009] (see Table 2). Patients treated with prucalopride were more likely to rate their treatment as effective compared with those treated with placebo (37–39% versus 20%; $p < 0.001$). Patients treated with prucalopride were more likely to have an improvement in PAC-QOL scores from baseline of ≥1 point compared with placebo at both 4 and 12 weeks ($p < 0.001$ for both time points). AEs are described below.

In the study by Camilleri and colleagues [Camilleri *et al.* 2008], 10 of 411 patients who received prucalopride reported a serious adverse event (SAE) compared with 8 of 209 patients who received placebo. There were no deaths in the study, although one patient treated with 2 mg of prucalopride developed a supraventricular tachyarrhythmia, although this patient had known mitral-valve prolapse and a history of supraventricular tachycardia. No patient in the placebo group stopped the medication due to diarrhea,

Figure 3. Structure of linacotide.

although 1.5–4.4% of prucalopride patients discontinued the medication due to diarrhea (2 and 4 mg doses, respectively). The authors reported that no differences were identified among the three groups with respect to serum chemistries, urinalyses, vital signs, EKG findings, or hematologic findings. Tack and colleagues [Tack *et al.* 2009] did not report any deaths in their study nor were any clinically significant differences found in serum chemistries, EKGs, urinalysis, or hematologic data. Discontinuation of the study medication due to AEs was reported in 6.7% of placebo-treated patients, compared with 6.3% of patients treated with 2 mg of prucalopride and 15.1% treated with 4 mg of prucalopride. Discontinuation AEs primarily consisted of headache, nausea, diarrhea, and abdominal pain and usually occurred within the first few days of treatment. Finally, Quigley and colleagues [Quigley *et al.* 2009] reported no deaths in their study, no differences in EKGs or lab parameters, and approximately 2% of patients in each of the three treatment groups reported an SAE (not statistically significant). The rate of study drug discontinuation due to AEs was slightly higher in the 4 mg prucalopride group (6%) compared to the 2 mg group (4%) and the placebo group (2%). AEs were the same as noted in the other two studies.

The reader is referred to a comprehensive review on the cardiovascular safety profile of 5-HT₄ agonists for further information [Tack, 2012].

Linacotide

Linacotide is a 14-amino-acid peptide that stimulates intestinal guanylate cyclase type-C (GC-C) receptors (see Figure 3) [Busby *et al.* 2005]. Linacotide is acid stable and protease resistant. In addition, bioavailability is low; it is undetectable in the systemic circulation at therapeutic doses. Linacotide mimics the action of endogenous guanylin (15 amino acids) and uroguanylin (16 amino acids), both of which activate the GC-C receptor [Currie *et al.* 1992; Hamra *et al.* 1993]. GC-C is expressed at high levels in the small intestine and colon, but low levels in the stomach. Activation of GC-C stimulates the production of cyclic guanosine monophosphate (cGMP) from guanosine triphosphate (GTP), which then increases the flow of electrolytes (HCO₃⁻ and Cl⁻) and water into the lumen of the GI tract (see Figure 4). This is associated with an increase in GI transit. In addition, stimulation of the GC-C receptor on intestinal epithelial cells and release of cGMP into the serosa leads to a reduction in visceral hyperalgesia [Bryant *et al.* 2005].

Figure 4. Proposed mechanism of action of linaclotide. GC-C, guanylate cyclase type-C; CFTR, cystic fibrosis transmembrane conductance regulator; cGMP, cyclic guanosine monophosphate; GTP, guanosine triphosphate. Illustration courtesy of Alessandro Baliani. Copyright © 2012.

The pharmacokinetic and pharmacodynamic effects of linaclotide acetate have been evaluated in a variety of models of intestinal transit and secretion. Bryant and colleagues [Bryant *et al.* 2010] reported the pharmacokinetic and pharmacodynamic characteristics of linaclotide in male

and female wild-type (wt) and GC-C null mice. Using competitive radioligand-binding assays, linaclotide was shown to act locally at GI GC-C receptors on the intestinal mucosal membranes. In this same paper, the authors reported that the beneficial effects of linaclotide on intestinal transit

Table 3. Summary of linaclotide clinical trials in chronic constipation.

	Johnston <i>et al.</i> [2009]		Lembo <i>et al.</i> [2010]		Lembo <i>et al.</i> [2011]		
					Trial 01*		Trial 303*
Percentage female	88%		92%		90%		87%
Mean age (years)	45.4				48		
Total randomized	42				630		642
Total completed	38						
Total analyzed	37				630		642
Mean CSBMs/week (baseline)			0.4		0.3		0.3
Mean SBMs/week (baseline)			2.3		1.9		2.0
CSBMs/week	Placebo	1.30	Placebo	0.5	Placebo	0.6	0.5
	100 µg	2.16	75 µg	1.5	145 µg	2.0 ^c	1.9 ^c
	300 µg	2.90	150 µg	1.6 ^a	290 µg	2.7 ^c	2.0 ^c
	1000 µg	3.19	300 µg	1.8 ^b			
SBMs/week			600 µg	2.3 ^a			
			Placebo	1.5	Placebo	1.1 ^c	1.1 ^c
			75 µg	2.6 ^a	145 µg	3.4 ^c	3.0 ^c
			150 µg	3.3 ^a	290 µg	3.7 ^c	3.0 ^c
			300 µg	3.6 ^b			
			600 µg	4.3 ^b			

^a $p \leq 0.01$; ^b $p \leq 0.001$; ^c $p < 0.0001$; *12-week data
CSBM, complete spontaneous bowel movement; SBM, spontaneous bowel movement

were lost in GC-C receptor knockout mice, demonstrating the specificity of linaclotide for this receptor [Bryant *et al.* 2010]. Pharmacokinetic studies showed that linaclotide was minimally absorbed and the oral bioavailability was shown to be approximately 0.10%. Using ligated intestinal loops in wt and GC-C null mice, linaclotide was shown to stimulate fluid secretion and cGMP production in wt mice, but not in null mice, supporting a direct linaclotide-mediated effect on GC-C receptors. The rate of GI transit was measured in mice following acute, oral dosing with linaclotide (100 µg/kg) or and vehicle by measuring progression of activated charcoal in the small intestine. In the vehicle group, GI transit was not different in the GC-C null mice compared with the wt mice in the vehicle group. GI transit was significantly accelerated in the linaclotide treated group compared with vehicle in the wt mice, but not in the mice lacking the GC-C. Gender did not significantly influence the effects on GI transit.

Busby and co-investigators [Busby *et al.* 2010] reported similar results of *in vitro* assays, competitive radioligand binding assays and *in vivo* experiments to characterize the *in vivo* and *in vitro* pharmacology of linaclotide in rats. They also reported on the *in vitro* binding and agonist activity to GC-C receptors of linaclotide in human colon carcinoma T84 cells. Both high- and low-affinity binding sites were identified in rat T84 cells and rat intestinal mucosal cells. In T84 cells at pH 7.0, linaclotide inhibited binding at the GC-C receptors in a concentration-dependent manner. In human T84 cells, linaclotide stimulated cGMP accumulation in a concentration-dependent manner and caused a significant increase of cGMP levels compared to those produced by either guanylin or uroguanylin. The effects of linaclotide on GI transit were studied in male and female rats. Linaclotide at doses of 5, 10 and 20 µg/kg significantly increased GI transit compared with vehicle-treated rats.

Box 1. Rome II definition of functional constipation (modified from Thompson *et al.* 1999).

At least 12 weeks, which need not be consecutive, in the preceding 12 months, with two or more of the following symptoms present:

- Straining in >25% of bowel movements
- Hard or lumpy stools in >25% of bowel movements
- Sensation of incomplete evacuation in >25% of bowel movements
- Sensation of anorectal obstruction/blockade in >25% of bowel movements
- Manual maneuvers to facilitate >25% of bowel movements (digital disimpaction)
- <3 bowel movements per week

Note that loose stools should not be present, and criteria for irritable bowel syndrome are not fulfilled.

Interestingly, two different animal models from two different laboratories demonstrated that linaclotide suppressed visceral hyperalgesia and colorectal allodynia [Eutamene *et al.* 2010; Johnston *et al.* 2009]. How linaclotide improves visceral pain is unknown, although it may be a result of increased cGMP. Finally, tissue culture studies demonstrated that linaclotide binds to GC-C receptors on human colon cells and stimulates cGMP production [Busby *et al.* 2005]. These results led to the clinical trials described below (see Box 1).

Johnston and colleagues were the first to investigate the safety, tolerability, and efficacy of linaclotide in patients with CC who met modified Rome II criteria (see Table 3) [Johnston *et al.* 2009]. In this multicenter, placebo-controlled pilot study 42 patients were randomized to one of three doses of linaclotide (100, 300, or 1000 µg) or placebo once daily for 2 weeks. On a daily basis for the 7 days preceding therapy and then during treatment, patients recorded daily bowel habits, including stool frequency, consistency according to the Bristol Stool Form Scale (BSFS), straining and completeness of evacuation, and subjective patient reported outcomes (i.e. abdominal discomfort, overall relief, and severity of constipation). Given the small sample size, the study endpoints were not intended to achieve statistical significance; however, there was a trend towards a dose-dependent increase in frequency of weekly SBMs and CSBMs. Stool consistency, straining, and patient reported outcomes also improved in all dosing groups. A total of 22 AEs were reported in 13 of 42 patients (30%) without significant

difference amongst the groups. All AEs were mild-moderate in severity and mostly GI in nature. Diarrhea was the most common side effect occurring in 13% of all study drug patients, but without a noticeable dose-dependent effect. No patient treated with placebo reported diarrhea as an AE.

These promising results led to a large multicenter, placebo-controlled study which involved 310 patients with CC as defined by modified Rome II criteria [Lembo *et al.* 2010]. Patients were randomized to one of four linaclotide dosages (75, 150, 300, or 600 µg) or placebo once daily for 4 weeks. The primary endpoint was the change in mean weekly SBM frequency from the 14-day pretreatment period to the 4-week treatment period. Patients were also analyzed using a responder definition of a weekly SBM ≥ 3 and in increase of ≥ 1 relative to baseline, for three of the four treatment weeks. Secondary endpoints included changes in stool consistency, straining, abdominal discomfort, and bloating. Lembo and colleagues noted that the frequency of weekly SBMs increased significantly in a linear response to increasing dosages of linaclotide (2.6, 3.3, 3.6, and 4.3 for linaclotide doses of 75, 150, 300, and 600 µg, respectively), compared with 1.5 for placebo ($p < 0.05$ for each linaclotide dosage group compared with placebo). The median time to first SBM, mean number of CSBMs, stool consistency, and severity of straining also demonstrated a significantly improved dose-dependent relationship compared with placebo. Subjective patient measures including abdominal discomfort, bloating, global measures of constipation, and health-related quality of life were significantly better for all linaclotide dosing regimens compared with placebo. During a 14-day post-treatment surveillance period, bowel habits were noted to trend towards baseline suggesting that linaclotide does not cause a rebound worsening of constipation symptoms. AEs were reported in 33.8% of patients receiving the study drug and 31.9% of placebo (n.s.). The most commonly reported AEs were GI-related, of which diarrhea was the most frequent (5.1%, 8.9%, 4.8%, and 14.3% in the 75, 150, 300, and 600 µg groups, respectively) versus 2.9% of placebo patients. Only two cases of diarrhea were graded as severe, both were in the 600 µg group and both resulted in cessation of treatment. Although these studies included only about 10% men and less than 20% nonwhites, linaclotide appears to be equally effective in these subgroups as the intention-to-treat population.

Figure 5. Structure of plecanatide.

The results of two parallel, randomized, placebo-controlled, double-blinded trials using either 145 µg or 290 µg linaclotide or placebo over 12 weeks in 1272 patients with CC were recently reported [Lembo *et al.* 2011]. Trial 01 consisted of 630 patients while trial 303 consisted of 642 patients (median age 48; 89% female). The primary endpoint of both trials was defined *a priori* as both three or more CSBMs/week and an increase of at least one CSBM/week from baseline for at least 9 out of the 12 weeks. Secondary endpoints included measurements of stool frequency, stool consistency, severity of straining, abdominal discomfort, bloating, and overall constipation severity. The authors reported that once-daily linaclotide produced early and sustained improvement in bowel and abdominal symptoms, SBMs, and CSBMs within the first week of treatment. For the 12-week study period the primary endpoint (12-week CSBM overall responder for ≥ 9 of 12 weeks) was met in both trial 01 (16.0%, 21.3% *versus* 6.0% for placebo, $p = 0.0012$ and $p < 0.0001$) and 303 (21.2% and 19.4% *versus* 3.3%, $p < 0.0001$). These benefits remained when the data was pooled and analyzed for weeks 1 through week 12. Secondary endpoints including CSBMs/week, SBMs/week, stool consistency, straining, constipation severity, abdominal discomfort, and bloating were superior to placebo and statistically significant in both studies for each dose of linaclotide. Trial 303 included a randomized 4-week withdrawal study that included 538 of the 642 patients. Patients initially treated with linaclotide were either continued on linaclotide or were switched to placebo, while placebo patients were switched to 290 µg linaclotide. CSBM rates for linaclotide-treated patients re-randomized to placebo decreased to placebo CSBM rates during the study, while those maintained on linaclotide had sustained CSBM rates (complete data not provided). CSBM rates of placebo patients allocated to linaclotide increased to levels seen during the primary treatment period (complete data not available). A rebound effect, characterized by a worsening of constipation symptoms, was not seen following cessation of linaclotide. A significant treatment effect on CC bowel and abdominal

symptoms and global assessments was found (r values 0.51–0.60, 0.46–0.59, and 0.44–0.59, respectively). Quality of life assessments, using the PAC-QOL instrument, showed an improvement in patients treated with linaclotide compared to those treated with placebo ($p < 0.01$). The authors reported one death in this study: it occurred due to an overdose of fentanyl and was not thought related to the study drug. SAEs occurred in 2.1% of patients treated with placebo, compared with 1.4–2.6% of those treated with linaclotide (145 and 290 µg doses, respectively). Discontinuation rates due to AEs were 4.2% in placebo-treated patients, compared with 7.9% in patients treated with 145 µg linaclotide and 7.3% in those treated with 290 µg of linaclotide. Discontinuation of the study medication and AEs were primarily GI-related, and the most common GI-related AEs were diarrhea, flatulence, and abdominal pain. No clinically significant differences were found among the three groups with regard to EKG results, vital signs, blood chemistries, urinalysis, or hematologic findings.

Plecanatide

Plecanatide (SP-304) is an experimental 16-amino-acid GC-C agonist presently in phase II/III trials for both CC and inflammatory bowel disease. Structurally and functionally, it is nearly identical to the human hormone uroguanylin save for an extra methylene at the third amino-acid position (Asp→Glu) (see Figure 5) [Solinga, 2011]. Binding of uroguanylin or plecanatide to transmembrane enteric receptors stimulates increased production of intracellular cGMP which activates the cystic fibrosis transmembrane conductance regulator (CFTR) and increases secretion of fluid and ions into the GI lumen. In a phase II, double-blinded, placebo-controlled, dose escalation, and repeated dose trial over 14 days, 84 patients who met modified Rome III criteria for CC were randomized to placebo or 0.3, 1.0, 3.0, and 9.0 mg of plecanatide (22 placebo, 62 plecanatide). CSBMs and SBMs, stool consistency, straining, abdominal discomfort, and overall relief were all improved. The median change of CSBMs was

3.0 *versus* 0.5 for patients receiving 1.0 mg plecanatide *versus* placebo (*p* value not provided; [Shailubhai, 2011]). A large multicenter trial is planned to study plecanatide in CC patients.

Other novel agents in development

Velusetrag

Velusetrag (TD-5108) is a highly selective 5-HT₄ agonist shown to increase colonic transit in animal models [Beattie *et al.* 2008]. GI transit was evaluated in a study of 60 healthy volunteers randomly assigned to receive 5, 15, 30 or 50 mg of velusetrag or placebo either as a single dose or over 6 days [Manini *et al.* 2010]. Single doses of velusetrag (30 and 50 mg), but not placebo, accelerated colonic transit, as measured by colonic filling at 6 hours and geometric center at 24 hours. Multiple doses of velusetrag (15–50 mg doses) accelerated gastric emptying compared with placebo (*p* = 0.002). In this same study, Manini and colleagues reported that velusetrag improved stool frequency and stool consistency in a subset of 11 patients with chronic constipation [Manini *et al.* 2010]. A recent phase IIB dose-ranging study (15, 30, 50 mg) in 401 adults with chronic constipation found that velusetrag improved stool frequency and stool consistency [Goldberg *et al.* 2008]. The most common side effects reported with diarrhea and headache. Large, randomized, placebo-controlled trials are required to confirm these intriguing results.

Chenodeoxycholate

In a study performed over 30 years ago, high-dose chenodeoxycholic acid (CDC; 750–1000 mg/day) caused diarrhea in patients being treated for gallstone disease [Mok *et al.* 1974]. This side effect could be used advantageously to treat patients with chronic constipation. To date, no study has been performed in patients with chronic constipation. However, a recent double-blind, placebo-controlled study of 36 women with IBS and constipation determined that CDC (either 500 mg or 1000 mg q day) accelerated colonic transit and loosened stool consistency [Rao *et al.* 2010]. Lower abdominal cramping was the most common side effect reported during this 4-day study. Larger dose ranging studies will be needed in patients with CC to determine whether the benefits demonstrated in this study of IBS patients can be replicated, and whether benefits can be

maintained over a longer period of time with an acceptable rate of side effects.

A3309

A3309 is a novel oral agent that inhibits the ileal bile acid transporter and consequently increases the flow of bile into the colon. It has been shown to increase colonic transit in a small study (phase Ib) of patients with chronic constipation [Simren *et al.* 2011]. In a double-blind, placebo controlled study of 36 women with chronic (functional) constipation, 14 days of treatment with 20 mg of A3309 improved colonic transit at 24 hours [Wong *et al.* 2011] and improved stool consistency. Colonic transit at 48 hours was accelerated using both a 15 and 20 mg dose, compared with placebo (*p* = 0.002 and *p* < 0.001, respectively). Patients reported improvements in stool consistency and straining. Gastric emptying in patients treated with A3309 appeared to be slightly delayed compared to placebo, although this was not statistically significant. AEs including lower abdominal cramping and pain in 36–50% of patients treated with A3309. Further trials are warranted to determine whether the efficacy can be maintained over a prolonged period of time, and whether side effects are short-lived and/or tolerable.

Summary

Chronic constipation is a highly prevalent disorder that all healthcare providers should feel comfortable diagnosing and treating. A thorough history and physical examination to uncover warning signs and symptoms of a serious underlying disorder, when combined with the Rome III criteria, can be used to confidently make the diagnosis of constipation. Many patients will have already tried over-the-counter agents before seeking out the advice of a healthcare provider. For these patients with persistent symptoms, lubiprostone has been shown to improve symptoms with minimal side effects. Although not currently available in North America, prucalopride has been shown to be safe and effective in three large phase III studies involving nearly 2000 patients. Mechanistic studies have demonstrated that prucalopride accelerates colonic transit, improves stool consistency, and reduces straining. Although fears exist about cardiovascular side effects from 5-HT₄ agonists, these appear unwarranted [Tack, 2012]. For those patients with persistent symptoms, several new therapeutic agents are in

development, and one (linaclotide) will likely be approved by the FDA for use in the United States in 2012. Linaclotide's mechanism of action is unique and the prospective, multicenter trials published to date show that it is efficacious at treating the multiple symptoms of constipation. Although not discussed here, linaclotide has been shown to improve abdominal pain in patients with IBS and constipation. The precise mechanism of linaclotide-induced pain relief is unknown, however one hypothesis is that cGMP modulates visceral pain. This concept is exciting and should provide a guide for future investigations into visceral pain. Other medications (velusetrag, plecanitide) hold promise, however it will likely be several years before the results of large, prospective studies are available for review. Finally, sacral nerve stimulation and colonic stimulation may hold promise for those patients who fail medical therapy. These therapies are currently investigational only and need to be subjected to rigorous testing before they can be recommended.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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