Motility disorders of the colon and rectum

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Purpose of review
Symptoms associated with disorders of the motility of colon and rectum are common problems in clinical practice. Advances in this field continue to expand our understanding of these disorders and provide new and different treatments with promising results.

Recent findings
This article reviews new advances in the past year on the measurement and diagnosis of colonic transit. Recently published data question the importance of dietary fiber in the prevention of colonic diverticulosis and diverticulitis, and support the efficacy of a number of different therapies aimed at improving colonic motility and visceral sensation in constipation and reversing the effects of opioid induced constipation with peripherally acting opioid antagonists.

Summary
The articles referenced in this review help inform the reader on new developments in the diagnosis and management of patients with colonic and rectal motility disorders.

Keywords
colonic motility, constipation, diarrhea, diverticular disease, scintigraphy, wireless motility capsule

INTRODUCTION

Symptoms related to disorders of the motility of colon and rectum are common problems in gastroenterology and primary care, occurring either as primary disorders or as secondary to other diseases (e.g. diabetes, Parkinson's disease) or treatments (e.g. opioids, antidepressants), and include common problems such as chronic constipation, diverticulosis, irritable bowel syndrome (IBS), and pelvic floor dyssynergia. IBS alone is one of the most common functional gastrointestinal disorders with an overall prevalence estimated at approximately 10% [1]. Although these patients often have abnormal colonic and rectal motility, the pathophysiology is much more complicated and seems to be a consequence of dysregulation of the brain–gut axis resulting in visceral hypersensitivity and altered intestinal motility and secretion [2,3]. Other abnormalities, including alterations in the intestinal microbiota and colonic immune activation, also appear to be important and may contribute to the altered motility and visceral hypersensitivity of these patients [2]. This article reviews the new guidelines for the measurement of the colonic transit and recent publications evaluating the advances in the diagnostic testing for colonic transit. We also review epidemiological studies evaluating the effectiveness of dietary recommendations in patients with diverticulosis. Finally, we review novel therapies for the treatment of constipation and other functional bowel disorders.

COLONIC TRANSIT TESTING

Disorders of colonic motility typically present with constipation or diarrhea, and often affect colonic transit time (CTT). Three methods of assessing CTT have been approved and validated by the American and European Neurogastroenterology and Motility Societies: radioopaque markers (ROMs), scintigraphy and wireless motility capsule (WMC) [4▪▪]. A brief review of recent advances in pelvic floor testing is also included.

Radioopaque markers

ROM is a traditional and widely used test indicated for patients with constipation, to differentiate

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KEY POINTS

- ROMs, CTS and WMC are the three effective methods currently approved and validated for colonic transit testing.
- The benefits of fiber and some restrictions in diet (nuts and corn) in patients with diverticulosis are now in doubt based on recent studies.
- MNX and alvimopan have demonstrated effectiveness in the treatment of constipation induced by opioids, without affecting analgesia.
- Linaclotide improved bowel and abdominal symptoms associated with irritable bowel syndrome with constipation for up to 26 weeks in phase III clinical trials.
- Elobixibat and LX1031 have shown promising results for the treatment of chronic idiopathic constipation and irritable bowel disease with diarrhea, respectively, in phase II trials.

between normal and slow CTT and to assess segmental transit times, and to evaluate the response to new treatments. Because pelvic floor dysfunction can cause slow CTT, anorectal physiological testing (i.e. anorectal manometry) should be considered in the appropriate patient prior to performing ROM [4▪▪]. ROM can also assist in the evaluation on unexplained diarrhea to exclude rapid transit, although its utility has not been well established. ROM is widely available, relatively well tolerated and inexpensive. Its main flaws include radiation exposure, the need for multiple visits for abdominal radiographs, and the lack of standardized protocols [4▪▪,5,6]. The mean CTT is 30–40 h, with an upper limit of normality of 70 h. Women often have longer maximal CTT (70–106 h) and may be influenced by menstrual cycle; also CTTs are generally shorter in healthy Asian populations than in Westerners, perhaps due, in part, to the difference in the consumption of fiber or spicy foods [4▪▪,5,7].

Colonic transit scintigraphy

Measurement of gastrointestinal transit with scintigraphy is only available in a limited number of specialized centers [8]. Colonic transit scintigraphy (CTS) is particularly useful to measure the whole gut and regional colonic transit in patients with diffuse disorders involving the stomach or small intestine, or with suspected colonic motility disorders, determining if the motor abnormality is diffuse or localized to a specific region. It has also been used in clinical trials to demonstrate response to therapy [4▪▪]. The test offers reproducible and accurate performance across a spectrum of common motility disorders, linking colonic transit measurements to biological processes, and provides correct prediction of outcomes in therapeutic interventions. The main limitations of this study are the limited availability and long duration of the test, expense, and the use of radiation, albeit minimal [4▪▪,7]. The results can be reported as overall colonic transit expressed as geometric center (weighted average of the isotope distribution within colon and stool), transit time in hours (T1/2), proximal colonic emptying, center of mass or percentage of radioactivity retained. A high geometric center implies fast colonic transit because the center of the activity has progressed to the left side of the colon or has been eliminated in the stool, whereas a low geometric center implies slow colonic transit because the center of the activity is in the proximal colon [7].

Wireless motility capsule

The newest modality to measure colonic transit is the WMC, which was approved by the Food and Drug Administration (FDA) in 2006 for the assessment of gastric emptying, and in 2009 for the colonic and whole gut transit time, in adults. WMC is indicated in patients with suspected motility disorders in more than one region of the gastrointestinal tract, and to distinguish slow from normal colonic transit. Measurement of combined small and large bowel transit time is performed as a surrogate measure of colonic transit in chronic constipation when CTT alone cannot be determined [4▪▪,7,9]. WMC can be performed as an outpatient without radiation exposure. Like the other measures of colonic transit it can also be used for testing colonic response to pharmacological agents [4▪▪,5,7]. However, device failure is reported in approximately 3% of cases and its use is not recommended in patients with pacemakers or defibrillators, swallowing disorders, suspected strictures or fistulae, or patients at high risk for strictures (e.g., postgastrointestinal surgery within the previous 3 months, Crohn's disease). This capsule continuously measures the temperature, pH, and pressure of its surrounding environment while traveling through the gastrointestinal tract until exiting the body. CTT less than 5 h is considered rapid, and when transit times exceed 59 h (range of normality: 10–59 h) is considered delayed [7].

Pelvic floor and rectoanal disorders

Anorectal manometry and X-ray defecography are the main techniques used to diagnose pelvic floor disorders [6]. Recently, additional testing including colpocystoenterodefecography, magnetic resonance (MR)-defecography, and ultrasonography of the pelvic floor are now available in some centers and may be particularly useful in patients with

pelvic organ prolapse. Likewise, MR neurography of the pelvic floor may be useful in detecting pudendal nerve entrapment neuropathy in patients with chronic pelvic pain [10]. Rectal scintigraphy has potential advantages as a diagnostic test in terms of quantitation and decreased radiation exposure, but there is controversy in the literature about its sensitivity and specificity [8].

DIVERTICULOSIS AND DIET

Diverticulosis is a very prevalent finding, especially among the aging population. By the age of 60 years, more than one-third of the population will develop diverticulosis, with the prevalence rising to more than two-thirds by 85 years of age [11▪,12]. Previously, the development of diverticulosis was attributed to low-fiber diets and age, but recent studies have questioned the traditional hypotheses. These studies suggest that although fiber may alleviate bowel symptoms, such as constipation, it does not reduce the development of diverticulosis or its complications. In similar cases, physicians commonly advise patients with diverticulosis to avoid eating nuts, corn, and popcorn, as they are believed to worsen the symptoms, likely inducing complications. A recent study has found evidence to refute the long-standing beliefs that nuts, corn, and popcorn among others may worsen symptoms and induce complications.

Diet and diverticulosis

In a recent observational cross-sectional study, of 2104 patients undergoing outpatient colonoscopy the prevalence of diverticulosis did indeed increase with age, but other findings were contrary to expected results [11▪]. Low dietary fiber was not associated with an elevated rate of diverticulosis, rather high dietary fiber intake was positively related to the presence of diverticulosis after adjustment for age, race, and BMI (prevalence ratio = 1.30). This association was found to be dose-dependent and also stronger in cases limited to three or more diverticula. Specific fiber subtypes, including grains (PR = 1.49; 95% CI, 1.09–2.04), insoluble fiber (PR = 1.64; 95% CI, 1.18–2.28), and soluble fiber (PR = 1.74; 95% CI, 1.24–2.45) were each significantly associated with having three or more diverticula. No associations were found between fat intake, red meat intake, physical activity or NSAID use and diverticulosis. Patient report of constipation was not positively related to diverticulosis. In fact, individuals with increased frequency of bowel movements seemed to be at a greater risk for diverticulosis. No association was found between bowel movement frequency and fiber intake comparing individuals with less than seven bowel movements per week and those who had seven or more, adjusting for sex and BMI. The major limitation with this study is potential for recall bias. Although these results are provocative, fiber may have beneficial effects on other chronic diseases including diabetes, cancer and cardiovascular disease and, therefore, it would be premature to instruct patients to reduce their current dietary fiber intake [13].

Nuts, corn, and popcorn and diverticulosis

In another study, the established belief that nuts, corn, and popcorn should be avoided by patients with diverticular disease was examined in 47 228 men, followed from 1986 to 2004 as part of the The Health Professionals Follow-up Study through biennial self-administered questionnaires [12]. The study found inverse associations between nut (multivariable HR = 0.80; 95% CI, 0.63–1.01; *P* for trend 0.04) and popcorn (multivariable HR = 0.72; 95% CI, 0.56–0.92; *P* for trend 0.007) consumption and the risk of diverticulitis, independent of age, BMI, dietary fat, fiber and red meat, physical activity, cigarette smoking, and the use of NSAIDs or acetaminophen. There was no association observed between corn consumption and diverticulitis. It has previously been presumed that these foods have poorly digested particles that are particularly abrasive, or may lodge within diverticula, and precipitate inflammation or bleeding. Likewise, there were no significant associations seen between nut, corn, or popcorn consumption and diverticular bleeding. An additional 2-year time lag analysis was performed to account for the possibility of a reduction in nut, corn, and popcorn consumption in response to symptoms of undiagnosed diverticular disease.

Results showed that the inverse association between frequent nut consumption and diverticulitis risk was strengthened (multivariable HR = 0.76; 95% CI, 0.61–0.96), and the popcorn association was lessened (multivariable HR = 0.89; 95% CI, 0.70–1.13; *P* for trend 0.21). Although the majority of the data was collected during a time when nuts were not perceived as a healthy food, current data instead indicates that a diet high in nuts may be protective for diverticulitis, as nuts contain anti-inflammatory properties, as well as high zinc and magnesium content that may positively affect colon health. There does not seem to be sufficient evidence for the high fiber content of nuts and popcorn explaining the inverse associations between these foods and diverticulitis. The results of this study

suggest that physicians should not recommend that patients with diverticular disease avoid consumption of nuts, corn, and popcorn.

NOVEL TREATMENTS

There are currently several new drugs being developed to address various motility disorders of the colon and rectum. These include an ileal bile acid transporter (IBAT) inhibitor, tryptophan hydroxylase (TPH) inhibitor, peripheral opioid antagonists, and guanylate-cyclase agonists. These will be discussed in further detail below.

Ileal bile acid transporter inhibitor

Inhibitors of the IBAT reduce the active ileal reabsorption of bile acids, resulting in an increased concentration of bile acid entering the colon, which stimulates colonic motility and secretion [14]. Elobixibat (A3309) is a potent and selective, minimally absorbed from the gastrointestinal tract, IBAT inhibitor. It has been tested in phase II trials with chronic idiopathic constipation patients [15,16▪]. The three studies published to date, one multicenter and two single-center, report similar results regarding safety and the efficacy of elobixibat when compared with placebo, in improving the number of spontaneous bowel movements, stool consistency, and decrease in straining [15,16▪,17]. However, there was no consistent amelioration of abdominal pain or bloating, except at the 15-mg dose [16▪,17]. Adverse effects were mainly of gastrointestinal origin (i.e., abdominal pain and diarrhea), and increased with higher doses particularly at the 15-mg dose. Further evaluation of elobixibat is needed to confirm the most appropriate and well tolerated treatment dose and the effects of long-term administration, as the longest trial just lasted 8 weeks [17].

Tryptophan hydroxylase inhibitor

LX1031 was developed as an oral TPH inhibitor that acts locally on the gastrointestinal mucosa, gaining access primarily to TPH in the intestinal lining and thereby inhibiting 5-HT synthesis by the enterochromaffin cells. In a phase II trial LX1031 has shown safety and good tolerance at two dose levels (250 and 1000 mg four times daily), and a significant increase in stool consistency in patients with nonconstipated IBS after 4 weeks of treatment with the higher dose. Nevertheless, the relief of abdominal pain and discomfort only showed significant improvement after the first week, but this effect was not maintained subsequently [18▪,19]. Further studies are needed to determine the optimal dose for efficacy. In retrospect, patients manifesting a reduction in urinary 5-HIAA excretion, a marker for TPH inhibition, of 15% or more showed improvement in multiple efficacy parameters, which suggests that it may be possible to identify patients who are most likely to benefit from treatment with LX1031 and/or optimize individual dosing by monitoring urinary 5-HIAA excretion [18▪].

Peripheral opioid antagonists

Opioid-induced constipation (OIC) is becoming more common as the prevalence of opioid use for chronic cancer-related and noncancer pain increases. The prevalence of chronic pain in the adult population is as high as 40%. Opioids not only result in constipation but also result in more diffuse bowel symptoms (e.g., abdominal pain, GERD, nausea, etc.), which is commonly called opioid-induced bowel dysfunction. Treatment of OIC has traditionally included stool softeners and osmotic and stimulant laxatives, which can be cumbersome for the patients and are often ineffective. OIC is largely mediated by μ-opioid receptors located in the gastrointestinal tract. These effects can be reversed by the μ-opioid receptor antagonists naloxone and naltrexone, but these agents also reverse the central effects of opioids, resulting in loss of analgesia. Two peripheral opioid receptor antagonists, alvimopan and methylnaltrexone (MNX), have recently been introduced that specifically target the gastrointestinal pharmacological action of opioids without reversing the central effects of opioids.

METHYLNALTREXONE

MNX, a quaternary ammonium derivative of naltrexone, has limited ability to cross the blood–brain barrier and, therefore, reverses peripheral opioid effects without affecting analgesia. MNX is currently available as a subcutaneous injection and is approved for the treatment of OIC in patients with advanced illness receiving palliative care whose response to laxative therapy has not been sufficient. Although multiple studies have been conducted with MNX, a recent study by Michna *et al.* [20▪] demonstrated that subcutaneous MNX provides significant relief of OIC in nonmalignant pain. Patients received subcutaneous MNX 12 mg either once daily or every other day or placebo. Assessments included bowel movement count, time of bowel movement, straining, sense of incomplete evacuation, and quality of life. Within 4 h of the first dose, 34% of patients in both MNX groups had spontaneous

bowel movements compared to 9.9% on placebo ($P < 0.001$). Both MNX groups had significant shorter times to first spontaneous bowel movement, greater increases in number of weekly spontaneous bowel movements, and quality of life [20▪]. This study confirms the efficacy of MNX in patients with OIC.

ALVIMOPAN

Alvimopan is an orally administered peripherally acting μ-opioid receptor antagonist that is currently approved for use to reduce postsurgical ileus. Like MNX, alvimopan does not reverse analgesia or cause opioid withdrawal symptoms. In one study performed with participants who required >30 mg oral morphine/day and reported fewer than three spontaneous bowel movements per week, alvimopan at different doses (0.5 mg twice daily, 1 mg once daily, 1 mg twice daily) was compared with placebo for 6 weeks [21]. In comparison to placebo, there was a statistically and clinically significant increase in mean weekly spontaneous bowel movement frequency in the initial 3 weeks of the study with all three doses of alvimopan tested. There were also improvements in other factors including straining, stool consistency, incomplete evacuation, and abdominal bloating/discomfort [21]. In summary, both alvimopan and MNX show similar efficacy in the treatment of OIC. Both agents are advantageous because they reverse the peripheral effects of opioids without affecting the central effects, that is analgesia, however, further long-term efficacy and safety data are still needed.

Guanylate cyclase agonists

Linaclotide is a peptide that activates the guanylate cyclase C receptor on the luminal surface of the intestinal epithelium, which results in secretion of chloride and bicarbonate into the intestinal lumen and reduction in visceral pain. Linaclotide was recently approved for use in adults with IBS with constipation and chronic constipation. In two phase 3 clinical trials involving patients with chronic constipation [22▪], linaclotide significantly increased the percentage of patients who reached the primary end point of three or more complete spontaneous bowel movements (CSBMs) per week, with an increase from baseline of at least one CSBM per week for 9 or more weeks of the 12-week treatment period. This end point was reached by approximately 20% of the patients who received linaclotide 145 or 290 μg once daily as compared with approximately 5% who received placebo ($P < 0.01$). Linaclotide increased stool frequency, improved stool consistency, and reduced straining, abdominal bloating, and discomfort compared with placebo. Diarrhea was the most common adverse event, which led to discontinuation of treatment in 4.2% of patients.

More recently results of two phase III clinical trials involving patients with IBS and constipation were published [23]. These studies, which compared linaclotide 290 μg once daily to placebo, were similarly designed except one was 26 weeks in duration, whereas the other trial was 12 weeks in duration followed by a randomized withdrawal period. The primary assessments in both studies were evaluated over the first 12 weeks of treatment. The FDA Responder Endpoint for IBS-C was included as one of the primary endpoints in both trials. This endpoint defines a patient who, in the same week, reported improvement of at least 30% in average daily worst abdominal pain score; and increase of at least one CSBM from baseline for 6 out of the initial 12 of weeks of treatment. In both trials a greater percentage of patients who received linaclotide 290 μg were responders than patients who received placebo. For the 26-week trial, 33.7% of linaclotide-treated patients met the FDA Responders Endpoint versus 13.9% of placebo-treated patients ($P < 0.0001$). Among linaclotide-treated patients in this study, 48.9% met the pain criterion of the FDA Responder Endpoint and 47.6% met the CSBM criterion, versus 34.5 and 22.6% of placebo patients, respectively. Secondary endpoints, including abdominal pain, bloating and bowel symptoms, were also significantly improved with linaclotide versus placebo ($P < 0.0001$). Statistically significant differences from placebo continued to be present throughout the 26 weeks of treatment. Diarrhea occurred more commonly in the linaclotide-treated patients, which caused discontinuation in 4.5% versus 0.2% of placebo patients. Plecanatide is another guanylate cyclase C agonist that is currently in clinical trials.

CONCLUSION

ROMs, CTS, and WMC are effective methods for detection of altered colonic transit, although scintigraphy is only available in some centers. Anorectal manometry and X-ray defecography are the main techniques for diagnosing pelvic floor disorders. Recent studies question the traditional hypothesis about the benefits of fiber in the development of diverticulosis and its complications, but further studies are needed before advising patients to reduce their dietary fiber intake. Novel therapies with local intestinal effects continue to be developed and show encouraging results.

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Conflicts of interest

A.L. is consultant for Ironwood, Forest, Salix and Prometheus.
S.M. has no conflicts of interest.
B.G. has no conflicts of interest.

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