Purpose of review  
Continuing advances in pharmaceutical development are providing an expanding array of treatment approaches for patients with chronic constipation. More comprehensive characterization of pancolonic motility carries the promise of improved understanding of the pathophysiology of this common disorder. Chronic constipation which responds poorly to laxatives may result from the use of drugs such as opioids, or from defecation disorders and advanced colonic dysmotility.

Recent findings  
This article highlights improved characterization of pancolonic motility, evidence of efficacy of established and novel drugs for both idiopathic and opioid-induced constipation and a new algorithm for the evaluation of patients with chronic idiopathic constipation who respond inadequately to available laxatives.

Summary  
The articles cited in this review inform the reader of new developments in the evaluation and treatment of patients with chronic constipation.

Keywords  
colic motility, constipation, laxatives, opioid antagonists, opioid-induced constipation

INTRODUCTION
Chronic constipation is a common complaint in all countries and it is presumed, but not proven, that disorders of colonic and/or anorectal function underlie the disorder. The vast majority of patients with constipation is not studied but is treated on an empirical basis with laxatives, which either increase intestinal water content directly or stimulate motility leading to shortened colonic transit and decreased water absorption.

This article reviews recent developments in the management of constipation and newer studies that advance our understanding of colonic motility in general. These include advances in characterizing pancolonic motility using high-resolution techniques, updates of newer laxatives and promotility agents for chronic idiopathic constipation (CIC), new approaches to the treatment of opioid-induced constipation (OIC), and a revised algorithm for evaluation of constipation which is unresponsive to standard laxatives.

HIGH-RESOLUTION COLONIC MANOMETRY
Dinning et al. [1] continue to refine their studies of pancolonic motility with spatiotemporal mapping. Using a new high-resolution fiberoptic manometry system with 72 sensors at 1 cm intervals, they recorded colonic motor activity in 10 healthy individuals when fasted and after a test meal. They identified four types of propagating motor patterns, most of which propagated in a retrograde fashion. Following a meal, the well characterized high-amplitude propagating contractions (HAPCs) were accompanied by an increase in retrograde cyclic motor patterns. The authors believe that propagating motor patterns may be generated by two independent sources, potentially of neurogenic or myogenic origin.

These studies offer further potential insights into colon physiology in health and constipation. This is not to infer that patients with severe intractable constipation require these studies or that the results of these studies can be used to guide management. Likewise, the wireless motility capsule which records from only a single moving transducer is not likely to illuminate underlying colon motor
The development of peripherally restricted µ-opiate receptor antagonists represents a major advancement in the treatment of opioid-induced constipation.

The demonstration of noninferiority of PEG-electrolyte vs. a high-affinity 5-hydroxytryptamine4 (5-HT4) agonist reaffirms the desirability of studies to compare new laxatives with established and inexpensive laxatives such as bisacodyl and polyethylene glycol to help guide laxative use in chronic idiopathic constipation (CIC).

Novel secretory drugs and high-affinity 5-HT4 agonists currently remain a second tier choice for CIC, but may have a more primary role in irritable bowel syndrome with constipation.

Patients with CIC refractory to available laxatives should be tested for a defecation disorder using both balloon expulsion and anorectal manometry before measuring colonic transit times.

The medical management of CIC continues to be suboptimal, with many patients expressing dissatisfaction with conventional therapies. As CIC is a symptom-based disorder, it is unclear whether this dissatisfaction is based on psychosocial or biologic factors, or both. Nevertheless, there continues to be a resurgence of interest in drugs that stimulate gastrointestinal motility through the 5-hydroxytryptamine4(5-HT4) receptor, as well as through other novel mechanisms.

There is a lengthy published record on the efficacy of prucalopride for CIC, as summarized in a meta-analysis published in 2011 [2]. Prucalopride is a high-affinity 5-HT4 receptor agonist, which is known to stimulate gastrointestinal motility. The drug has yet to be approved for use in the United States, although it is widely used in Europe. A recent publication [3] demonstrated the efficacy of prucalopride 2 mg daily in a randomized controlled study involving 358 men (38% achieved the primary endpoint vs. 18% placebo controls over a 12-week treatment period). This extends and confirms previous studies of prucalopride on women with CIC.

A potentially more important study compared prucalopride with 26 g of polyethylene glycol (PEG)-electrolyte administered as a split dose for 4 weeks in a noninferiority analysis [4]. With 120 patients in each treatment arm and more than 99% compliance with therapy, the proportion of patients achieving the primary endpoint of more than three complete and spontaneous bowel movements (SBM) in the last week of therapy was higher with PEG (67 vs. 57%), as was the proportion of patients achieving secondary endpoints. In an accompanying editorial, Ford [5] raised the provocative issue of whether future studies in CIC should continue to be placebo controlled or should include a comparator group consisting of one of the effective but inexpensive laxatives such as PEG or bisacodyl. As we attempt to control healthcare costs, comparator studies will be important in deciding which new drugs should be available as first-line agents to most patients with CIC.

Lubiprostone and linaclotide are available for CIC and irritable bowel syndrome with constipation (IBS-C). A recent systematic review identified three randomized placebo-controlled studies of linaclotide in IBS-C encompassing 1773 patients [6]. Their conclusion was that there was ‘moderate confidence that linaclotide is moderately effective compared to placebo for improving typical symptoms of IBS-C’.

Linaclotide was estimated to reduce the number of failures to achieve symptom relief by 165/1000 patients, although this gain was offset by the need to discontinue therapy because of diarrhea in 31/1000 patients.

Plecanatide is another secretory agent similar to linaclotide and also works as an agonist of the GC-C receptors, uroguanylin and guanylin, to activate guanylate cyclase C. This increases intestinal secretion of chloride via the cystic fibrosis transmembrane conductance regulator pump. Early studies suggest that plecanatide, similar to linaclotide, may be effective for CIC and also IBS-C and may improve abdominal pain independent of stool frequency. The first human study to be published used nine different doses in healthy controls; there was minimal, if any, drug absorption, the incidence of diarrhea was not different from placebo, and increased side-effects occurred only at high doses [7]. A preliminary phase 2a study showed ‘impressive and beneficial improvement in all categories of constipation and Bristol stool form scores’ with benefit plateauing at the 1 mg dose [8]. It is likely that secretory agents will remain a second tier option for CIC but may have a more prominent role in IBS-C for which there are fewer alternatives to treatment.
OSMOTIC AGENTS
It is always reassuring when inexpensive and traditional treatments are validated in well controlled randomized trials. This is illustrated by a recent study of the efficacy of a magnesium sulfate-rich natural mineral water in women with CIC. This product (known as Hépar) has been marketed in France since 1930 [9] and contains magnesium 119 mg/l and sulfate 1550 mg/l, among others. The daily consumption of 1 l Hépar-reduced constipation over a 4 week period by 37.5 vs. 21% for those consuming 1 l of a low mineral natural water; there were no serious side-effects. Previous studies in children had shown that high doses of magnesium sulfate (>2000 mg/day) were as efficacious as PEG to improve frequency and consistency of stools [10]. This product would appear to be a possible first tier option for constipation in addition to stimulant laxatives and PEG.

OPIOID-INDUCED CONSTIPATION
An excellent review on the subject of constipation induced by opioids highlighted the dramatic increase in the use of opiates and opioids for chronic pain over the past two decades [11]. An estimated 40–90% of patients who use opioids have constipation and other gastrointestinal side-effects [12]. Opioids delay gastrointestinal transit, stimulate nonpropulsive motor activity, increase intestinal tone, increase fluid absorption by prolonging contract time for absorption to occur and decrease secretion of electrolytes and water into the intestinal lumen. A recent systematic review of treatment for OIC concluded that three different μ-opioid receptor antagonists – methylnaltrexone (six trials, 1610 patients), naloxone (four trials, 798 patients) and almivopram (four trials, 1693 patients) were all superior to placebo for OIC [13]. Currently, the use of methylnaltrexone is restricted by the need for subcutaneous injection only in patients with medically advanced illness, whereas almivopram is indicated only to shorten the duration of postoperative ileus [12]. Chronic use of naloxone alone has not been approved for use in the United States.

Recent studies support the use of three additional pharmacologic agents in the treatment of OIC; two include peripherally restricted μ-opiate receptor antagonists, whereas the third is the intestinal secretory agent, lubiprostone.

A recently published study supports the efficacy of lubiprostone to treat OIC in patients with chronic pain that is not attributable to cancer [14]. In a multicenter randomized, placebo-controlled trial, 210 patients with OIC were given lubiprostone 24 μg twice daily and 208 patients were given a placebo over a 3-month trial period. Approximately two-thirds of patients in each arm completed the trial and the primary endpoint was the change in SBM frequency at week 8 compared with baseline. Mean changes were approximately one SBM/week higher in patients treated with lubiprostone compared with placebo; this was statistically significant at 8 weeks but not at 12 weeks because there were fewer patients analyzed at 12 weeks. Statistically significant changes with lubiprostone were also seen in stool consistency, severity of constipation, straining and abdominal discomfort, but not bloating or bowel regularity. Overall effectiveness was rated as slightly but significantly higher by patients taking drug vs. placebo (mean was about 0.4 higher than placebo on a 0–4 scale, wherein 0 was not effective and 4 was extremely effective). The percentage of patients in each group who achieved the primary endpoint was not provided. Nausea occurred in 16.8% of patients (5.8% placebo), diarrhea in 9.6% (2.9% placebo), and abdominal distress in 8.2% (2.4% placebo), all statistically significant.

A more biologically plausible approach to OIC is to combine a strong opiate agent with an effective opioid receptor antagonist which will not counteract the benefits of pain reduction. An example of this is oxycodone/naloxone. Naloxone is an opioid receptor antagonist that exhibits a local effect on GI opioid receptors but is nearly completely inactivated by the liver after oral administration. A timely review that summarized the use of oxycodone/naloxone in patients with chronic pain (nonmalignant pain and cancer-related pain) was recently published [15]. An initial dose of 10/5 mg or 20/10mg twice daily is often effective and the drug is titrated to a maximum of 40/20 mg twice daily with the goal of achieving effective analgesia and acceptable adverse effects. The FDA has just approved an extended-release formulation of oxycodone/naloxone (Targiniq ER, Purdue Pharma LP, Stamford, Connecticut, USA) as an ‘abuse deterrent’ agent for use in ‘pain severe enough to require daily, around the clock, long-term opioid treatment, for which alternative treatment options are inadequate’.

A variation on this theme is the development of naloexogol, a pegylated derivative of naloxone, which limits the ability of naloexogol to cross the blood–brain barrier so that it acts only on peripheral μ-opioid receptors. In a phase 2, randomized, double-blind controlled trial that tested doses of 5 mg, 25 mg, and 50 mg given once daily, statistically significant increases in SBM per week were observed for the two higher doses vs. placebo [16]. Adverse effects were increased in patients receiving 50 mg daily but most adverse effects with the 5 mg
DEFECTION DISORDERS

Many patients with severe intractable constipation have either a defecatory disorder, known as dyssynergic defecation or isolated slow transit constipation, known as ‘colonic inertia’. The classical diagnostic approach to such patients has been to perform both colonic transit using radiopaque markers, and anorectal manometry (ARM) (or electromyography) with balloon expulsion. A recent technical review proposes a shift in the algorithm for diagnostic testing [17**]; another study confirms the validity of the balloon expulsion test (BET) [18].

The new technical review on constipation released by the American Gastroenterological Association suggests that patients with intractable constipation should initially undergo ARM and the BET, without a colon transit study [17**]. There were two reasons advanced for this position. First, up to 50% of patients with dyssynergic defecation have slow colonic transit, many of whom will normalize after successful treatment of the dyssynergic defecation. If initial testing is normal or if patients normalize the dyssynergic pattern with biofeedback but symptoms persist, a colon transit study should be performed to identify patients with slow transit. If patients with dyssynergic defecation respond clinically to biofeedback, colon transit testing is not necessary. This presumes that there are experienced laboratories that perform both studies when evaluating these patients. Unfortunately, no single test is sufficiently definitive to make a diagnosis of dyssynergic defecation.

A recent study was designed to test the reproducibility and agreement of the BET with ARM or EMG [18]. In a single center, 286 consecutive patients with chronic constipation and 40 healthy controls underwent BET on two occasions less than 1 month apart. Patients also underwent ARM and EMG; 47 patients with conflicting manometry and BETs underwent defecography.

All healthy controls passed a 50 ml water-filled balloon within two minutes (93% within 1 min), with perfect reproducibility, thus establishing the upper limit of normal. One hundred and forty-five patients had a normal BET and 141 were abnormal, also with perfect reproducibility. The level of agreement between BET and manometry was 78% and between BET and EMG was 83%. Thus, the BET is an office-based procedure, which is a reliable first test for dyssynergic defecation; if abnormal, ARM and/or defecography can be used to determine why expulsion is abnormal in a patient with chronic refractory constipation. Balloon expulsion alone or manometry alone is insufficient to evaluate a patient with suspected dyssynergic defecation.

CONCLUSION

The most recent therapeutic advances in chronic constipation are for the treatment of OIC, with the recent release of a combined opiate/opiate antagonist, the development of a pegylated opiate antagonist, and evidence of efficacy for lubiprostone. Although a number of new laxatives have shown efficacy for CIC, the demonstration of noninferiority of an inexpensive laxative vs. prucalopride underscores the need for more comparator studies of new and expensive drugs vs. effective, inexpensive laxatives such as bisacodyl and PEG. This will guide laxative use in CIC and help to better manage healthcare expenditures. The demonstration of efficacy of a magnesium sulfate rich natural mineral water in women with CIC demonstrates that newer and more expensive treatments are not necessarily better than older and inexpensive remedies for this very frequent condition.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

A.W. has served as a consultant to the following companies: Forest Lab, Ironwood, Takeda/Sucampo. None.
REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest
** of outstanding interest


An important study showing noninferiority (and perhaps superiority) of an established inexpensive laxative to a new 5HT4 agonist which is as yet not available in the United States. Newer is not always better but is invariably more expensive.


A succinct provocative editorial commenting on reference (Cinca) advocating the need for future comparator studies of new agents for constipation with established effective laxatives.


This article and its companion study [16] provide data to support this novel peripheral μ-opioid receptor antagonist to treat OIC.


This is the most recent evidence-based comprehensive review on this subject.